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Dementia risk estimates associated with measures of depression: a systematic review and meta-analysis

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ABSTRACT

Objectives: To perform a systematic review of reported HRs of all cause dementia, Alzheimer's disease (AD) and vascular dementia (VaD) for late-life depression and depressive symptomatology on specific screening instruments at specific thresholds.

Design: Meta-analysis with meta-regression.

Setting and participants: PubMed, PsycInfo, and Cochrane databases were searched through 28 February 2014. Articles reporting HRs for incident all-cause dementia, AD and VaD based on published clinical criteria using validated measures of clinical depression or symptomatology from prospective studies of general population of adults were selected by consensus among multiple reviewers. Studies that did not use clinical dementia diagnoses or validated instruments for the assessment of depression were excluded. Data were extracted by two reviewers and reviewed by two other independent reviewers. The most specific analyses possible using continuous symptomatology ratings and categorical measures of clinical depression focusing on single instruments with defined reported cut-offs were conducted.

Primary outcome measures: HRs for all-cause dementia, AD, and VaD were computed where possible for continuous depression scores, or for major depression assessed with single or comparable validated instruments.

Results: Searches yielded 121 301 articles, of which 36 (0.03%) were eligible. Included studies provided a combined sample size of 66 532 individuals including 6593 cases of dementia, 2797 cases of AD and 585 cases of VaD. The increased risk associated with depression did not significantly differ by type of dementia and ranged from 83% to 104% for diagnostic thresholds consistent with major depression. Risk associated with continuous depression symptomatology measures were consistent with those for clinical thresholds.

Conclusions: Late-life depression is consistently and similarly associated with a twofold increased risk of dementia. The precise risk estimates produced in this study for specific instruments at specified thresholds will assist evidence-based medicine and inform policy on this important population health issue.

Strengths and limitations of this study

- This study used a robust methodology that included a very broad search of the literature using clearly defined search terms and stringent inclusion and exclusion criteria.
- Particular care was taken to assess study characteristics so only studies that used compatible exposure and outcome measures would be combined.
- Detailed subanalyses were conducted to provide estimates for specific tools at specific thresholds.
- Study quality, publication bias and influence of relevant factors were formally investigated by meta-regression.
- The study was limited by the relatively small number of articles with relevant data published in this domain and, particularly so for vascular dementia, and by the fact that the Centre for Epidemiological Studies Depression scale (CES-D) was the only instrument that could be analysed separately.

INTRODUCTION

In a clinical environment where no cure for Alzheimer's disease (AD) and other dementias is available or likely to be developed in the near future, and in the context of a growing ageing population it is increasingly important to consider the potential of preventative approaches to decrease the impact of these debilitating conditions.[1 2] This requires the identification of risk factors and estimation of the magnitude of their effect, but critically it also requires the availability of reliable measures of risk exposure based on specific, validated instruments so individuals at higher risk can be identified and interventions and/or treatment can be calibrated at the individual level. Moreover, evidence-based medicine requires that clinical advice and decision-making be informed by precise and reliable evidence based on validated

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instruments at known thresholds.[3] Unfortunately, this evidence is not available.

A link between late-life depression and dementia has already been established and population-level risk estimates are available. However, results from studies investigating this question have important limitations.[4–6] Of three available meta-analyses on this topic, none has reported on risk measures related to specific instruments. Current evidence has been produced by combining findings based on different instruments and using both continuous measures of depressive symptomatology and categorical classification of major or minor depression with all three systematic reviews including findings based on self-report.[4–6] In addition, some of the available meta-analyses combined findings from studies using outcome measures of dementia based on accepted diagnostic criteria (eg, Diagnostic and Statistical Manual (DSM), National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)) with those of studies using criteria of unclear validity or relating to Mild Cognitive Impairment (MCI) and not dementia.[4] In at least one instance findings unrelated to dementia (cognitive decline in non-demented participants) were included in the analyses.[4] These methodological limitations have likely led to less reliable estimates of risk which are not clearly attributable to single screening instruments with known clinically relevant cut-offs.

The aim of this study was therefore to systematically review the literature on dementia risk for late-life depression and conduct meta-analyses pooling separately compatible findings from population studies using either continuous measures or specified cut-offs on validated instruments (eg, Centre for Epidemiological Studies Depression scale (CES-D)) to assess depression status and only in those studies which relied on widely accepted clinical criteria for dementia (eg, DSM-IV). Other aims included estimating and reporting relative risks (RRs) for dementia subtypes including AD and vascular dementia.

METHODS

This systematic review and meta-analysis follow the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[7 8]

Search strategy

We conducted a systematic literature search of PubMed, PsycInfo and Cochrane databases for studies describing the association between depression (defined by self-reported scales or clinical diagnoses) and dementia incidence published between 1996 through 28 February 2014. Details of search terms are presented in online supplementary table ST1. In summary, we combined two sets of search terms which identified articles relating to (1) depression, anxiety (because of its comorbidity with depression), or medication for these conditions AND (2) measures of cognition or diagnosis of any type of dementia. Searches were restricted to human studies and articles published in English. In addition, we searched the reference lists of identified relevant publications and reviews. Searches were conducted by experienced and qualified researchers following our published methodology.[9–11] All articles were reviewed for inclusion by two reviewers (JY and SK). An independent review of all articles was conducted by a second set of reviewers (KJA and NC). Any disagreement was resolved by consensus among all reviewers.

Selection criteria and article screening

The study inclusion criteria ensured that all articles included in the review met the Oxford Centre for Evidence-Based Medicine Level of Evidence 1B (http://www.cebm.net). Studies included following article screening were required to be prospective, longitudinal, population-based studies with a minimum follow-up period of 1 year. Studies were required to measure depression at baseline or during a follow-up period that preceded the final follow-up examination. Baseline depression was required to be measured using a standardised assessment tool with articles relying on self-report of depression diagnosis excluded from the analysis. The outcome measure had to include dementia. Studies were required to have screened for dementia at baseline unless the sample mean age at baseline plus two SDs was less than 60 years old. Cross-sectional, experimental and clinical studies and studies with a sample size of less than 100 and those not reporting on original published peer-reviewed studies were excluded to ensure only research of high quality would be considered. We identified articles eligible for further review by performing an initial screen of titles and abstracts, followed by a full-text review.

Data extraction

Data relating to depression and dementia diagnosis were extracted by two reviewers (JY and SK) from included articles for potential meta-analysis. Information extracted included: study design (sample source, number of participants and observation period), sample characteristics (country, percentage female, average age, age range, years of education, dropout rate), measurement of depression (measurement scale used and/or clinical criteria), covariates included in statistical models, dementia assessment and clinical criteria, and unadjusted and/or adjusted estimates of associations. Where results for more than one follow-up period were reported for the same study, the estimate from the longest follow-up was selected. Adjusted results were used where available. Data extraction was checked by a third reviewer (NC). Where insufficient data were available in articles meeting the inclusion criteria authors were contacted directly.

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Statistical analysis

We used HRs as common measure of association across studies and considered RRs as equivalent since it has been shown that for rare events they can be considered equivalent.[12] We assessed heterogeneity across studies with the Q statistic (with p<0.10 being suggestive of significant heterogeneity) and the I^2 statistic (values of 25%, 50% and 75% were indicative of low, medium and high heterogeneity). The HRs were pooled using the DerSimonian-Laird random-effects model[13] as the fixed-effects model is regarded as inappropriate in this type of meta-analysis where study design and methodology vary substantially.[14] Sensitivity analyses were conducted to identify studies that excessively contributed to heterogeneity with the leave-one-out method. The possible presence of publication bias was assessed through visual inspection of funnel plots, with the 'trim and fill' method,[15] and with the 'fail-safe' method.[16] In addition, sensitivity analyses were conducted to evaluate the influence of selected study and participants characteristics on results. Analyses were conducted in R V.3.1[17] using the metafor package V.1.9.3[18] and Review Manager V.5.1.[19]

Data synthesis

Data were pooled separately across studies for continuous and categorical measures of depression predicting all-cause dementia, AD or vascular dementia (VaD). Least specific analyses including studies using more diverse measures of depression were conducted first, followed by more specific analyses which focused on single instruments and/or on single cut-offs. Studies were considered compatible for combined analyses if (1) they provided risk estimates for the same type of measure (categorical or continuous) (2) they reported on instruments and cut-offs that would be widely considered as similar and comparable (eg, the long and the short form of the CES-D which have been validated against each other or instruments at specific thresholds validated against clinical criteria) (3) they estimated the risk for the same type of dementia (all-cause, AD or VAD) (4) they did not report on the same cohort. For continuous depression measures, data from all compatible studies were pooled in a first step followed by analyses including only instruments used to assess depressive symptomatology with a similar range (eg, CES-D range 0–60 and Hamilton rating scale for depression (HAM-D) 0–54). For categorical depression measures, data from all compatible studies using validated cut-offs (eg, CES-D≥20) or clinical diagnoses based on accepted criteria (eg, DSM-IV) were pooled in a first step. In studies which used the CES-D and reported on multiple cut-offs, estimates for a cut-off of 20/21 were used as this threshold has been reported as optimum for screening for major depression[20] (Note, however, that Fuhrer *et al*[21] have used a threshold of 17 for men and 23 for women because French validation studies have found these cut-offs most sensitive for clinical depression in their population and therefore we have considered them compatible but also conducted sensitivity analyses without this study). This was followed by analyses based on single instruments at a specific cut-off. Studies which exclusively reported an outcome of AD and/or VaD were not pooled in all-cause dementia analyses. Studies using the short form of CES-D with a cut-off of 10 were pooled with those using the long form with a cut-off of 16 as the psychometric properties of these two forms have been found to be comparable.[22] Studies were evaluated for methodological quality using the Newcastle-Ottawa scale.[23] Influence of study characteristics on pooled estimates, including study quality, proportion of females, length of follow-up, and sample mean age, was investigated by meta-regression.

RESULTS

Literature search

The search strategy identified 121 301 unique citations. After initial screening based on titles and abstracts 700 publications remained for further assessment. After close inspection of these articles and application of inclusion and exclusion criteria a further 565 articles were excluded (figure 1). Of those, 99 publications did not report relevant data or necessary data could not be extracted or obtained from authors, leaving 36 publications reporting on 29 unique cohorts for meta-analysis. Among included articles two were obtained from reference lists.

Of the 36 articles included 28 studies reported results on all-cause dementia, 28 studies on AD, 10 studies on VaD and surveyed a total of 66 532 participant including 6593 participants with all-cause dementia, 2797 with AD, and 585 with VaD. Regions of origin of participants included Europe (n=19), North America (n=13 studies), South Korea (n=2) and China (n=1). We considered the results as adequately adjusted if they were adjusted for at least age and education, but where available, we included the more fully adjusted models in analyses. Most studies adjusted for age, sex and education (n=21).

Multiple reports

Findings based on the same cohort were reported multiple times for six studies covered by 14 separate articles. When multiple reports were available for the same cohort, a risk estimate from only one publication was used in any single analysis. The most appropriate estimates were selected based on recency, sample size and methodology. When different articles from the same cohort reported on different depression measures (eg, continuous vs categorical, different cut-off, different diagnostic tools) or on different diagnostic outcomes (dementia, AD and VaD) estimates from the same cohort were sometimes used in different analyses (but never in combination).

Study characteristics

Characteristics of the 36 selected studies are presented in table 1. The assessment of depression was most frequently

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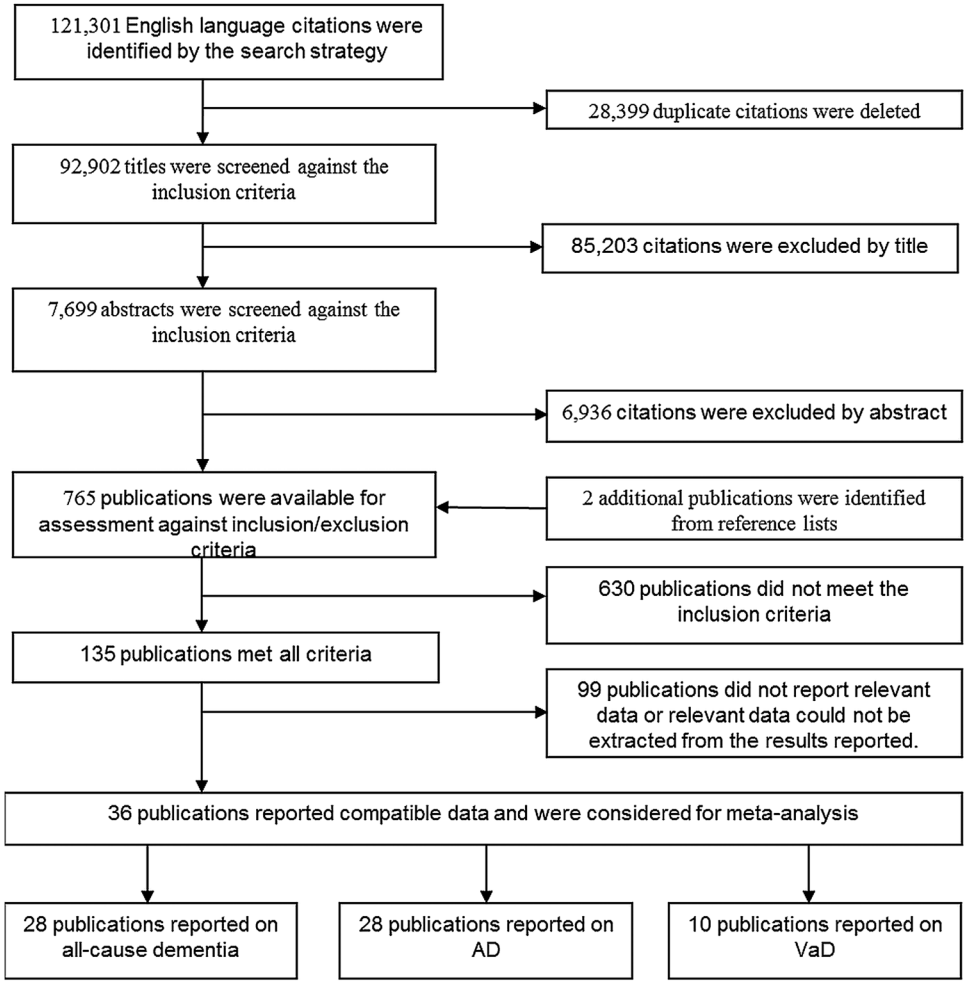

Figure 1 Flowchart of the search and study selection process. AD, Alzheimer's disease; VaD, vascular dementia.

based on: CES-D (n=17), Geriatric Mental State (GMS) (n=4), Geriatric Depression Scale (GDS) (n=3), HAM-D (n=2), Comprehensive Psychopathological Rating Scale (CPRS) (n=1), Neo (n=1), Symptom Checklist (SCL)-90 (n=1), clinical diagnosis (DSM-III/IV, n=5; Composite International Diagnostic Interview (CIDI), n=1), or international classification of diseases (ICD)-9 (n=1). Dementia diagnosis was most frequently established based on DSM-III/IV criteria (n=22), GSM-AGECAT (n=2), ICD9/10 (n=2) or Cambridge Cognition Examination (CAMGOG) (n=1). AD diagnosis was most frequently established based on National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (n=22) or DSM-III/IV (n=3) criteria. VaD diagnosis was based on National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) (n=8) or DSM-III/IV (n=2) criteria.

Study quality rating

Most studies were of excellent quality as attested by the scores ranging from 7 to 9 on the Newcastle-Ottawa scale (maximum 9; see online supplementary table ST2). Five of 36 studies were rated as not representative of the population mostly because they only reported on one gender. Eleven studies did not control for at least age and sex together, while only four studies did not control for other factors. Five studies did not fully account for all participants.

Summary risk estimates

Summary HRs for different measures of depression (continuous measures of symptomatology or categorical clinical thresholds), and different dementia outcome categories (all-cause dementia, AD and VaD) are presented in table 2. Sufficient data were only available for the CES-D using a cut-off of either 20 or 16 to conduct subanalyses on individual scales at specified thresholds. More detailed statistical outputs for all analyses are presented in online appendix SA1.

Depression and all-cause dementia risk

Risk estimates were first pooled across 10 studies[24–32] which assessed depression symptomatology as a continuous measure and a diagnosis of all-cause dementia as outcome. Instruments used to assess depression

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Table 1 Characteristics of included studies (n=36).

Author, year (number of participants)	Country (ethnic origin)	Follow-up years (SD)	Age years (SD)	Female (%)	Education, years (SD)/ level	Drop-out rate (%)	Baseline cognition score (SD)	Depression measure (cut-off)	Baseline depression score (SD)	Dementia diagnosis and criteria (number of cases)
Barnes *et al*, 2012 (n=13535)	USA (24.2% non-white)	6.0 (NR)	81.1 (4.5)	57.9	85.6% with high-school or higher	55.46%	NR	ICD-9	NR	Dementia (ICD9, n=3046) AD (ICD9, n=749) VaD (ICD9, n=314)
Becker *et al*, 2009 (n=288)	USA (17.4% non-white)	7.1 (NR)	77.5 (3.7)	63.2	61.5% with high-school or higher	34.7%	NR	CES-D-SF (≥10)	NR	AD (NINCD-ADRDA, n=48)
Blasko *et al*, 2010 (n=284)	Austria*	2.5 (NR)	78.3 (0.5)	~56.5	10.6 years (2.2)	14.8%	28.1 (1.4) MMSE	GDS (continuous)	1.6 (1.6)	AD (NINCDS-ADRDA, n=33)
Chen *et al*, 1999 (n=803)	USA (3% non-white)	4.5 (NR)	73.7 (5.0)	60.0	61.4% with high-school or higher	15.8%	24 (NR) MMSE	mCES-D (continuous)	NR	Dementia (DSM-III-R, n=78) AD (NINCDS-ADRDA, n=64)
Chen *et al*, 2008 (n=1329)	China (NR)	1.0 (NR)	>65 (NR)	NR	NR	27.8%	NR	GMS-AGECAT	NR	Dementia (GMS-AGECAT, n=75)
Chen *et al*., 2008 (n=2157)	UK (NR)	4.0 (NR)	>65 (NR)	NR	NR	58.7%	NR	GMS-AGECAT	NR	Dementia (GMS-AGECAT, n=176)
Dal Forno *et al*, 2005 (n=1357)	USA† (NR)	6.1 (NR)	65.5 (12.0)	42.4	16.8 (2.7)	NR	NR	CES-D (continuous, ≥20, ≥16)	7.1 (6.8)	Dementia (DSM-III-R, n=125) AD (NINCDS-ADRDA, n=107)
Devanand *et al*, 1996 (n=478)	USA‡ (70% non-white)	2.54 (1.12)	~72 (NR)	~70	10.4 (4.8)	41.6%	NR	HAM (continuous)	4.8 (4.8)	Dementia (DSM-III-R, n=61) AD (NINCDS-ADRDA, n=57)
Dotson *et al*, 2010 (n=1113)	USA† (10.5% non-white)	23.6 (NR)	52.7 (18.8)	42.3	16.6 (2.8)	NR	NR	CES-D (≥16)	NR	Dementia (DSM-III-R, n=142) AD (NINCDS-ADRDA, n=96)
Fuhrer *et al*, 2003 (n=3777)	France (NR)	8.0 (NR)	75.2 (6.9)	58.3	62.9% with primary school certificate or higher	37.4	25.6 (3.7) MMSE	CES-D (≥23 females, ≥17 males)	10.2 (9.3)	Dementia (DSM-III-TR, n=280) AD (NINCDS-ADRDA, n=200) VaD (n=37)
Gatz *et al*, 2005 (n=766)	Canada§ (*NR*)	5 (NR)	74.5 (6.0)	61.7	10.4 (3.2)	35.4	NR	CES-D (continuous, ≥13, ≥16, ≥17, ≥21)	6.1 (7.0)	Dementia (DSM-III-R, n=56) AD (NINCDS-ADRDA, n=36)

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Table 1 Continued

Author, year (number of participants)	Country (ethnic origin)	Follow-up years (SD)	Age years (SD)	Female (%)	Education, years (SD)/ level	Drop-out rate (%)	Baseline cognition score (SD)	Depression measure (cut-off)	Baseline depression score (SD)	Dementia diagnosis and criteria (number of cases)
Geerlings *et al*, 2008 (n=486)	Netherlands (NR)	5.9 (1.6)	73.5 (~7.5)	49.0	2.9 (1.6) on 8-point scale (from no primary to tertiary)	NR	27.7 (2.1) MMSE	CES-D (≥16)	NR	Dementia (CAMDEX, n=44) AD (NINCDS-ADRDS, n=33)
Geerlings *et al*, 2000 (n=1911)	Netherlands¶ (NR)	3.2 (NR)	73.1 (5.5)	62.3	8.6 (2.6)	39.3%	NR	GMS-AGECAT	NR	AD (DSM-IV, n=53)
Goveas *et al*, 2011 (n=6376)	USA (13% non-white)	5.4 (1.6)	70.1 (3.8)	100	92.8 with high school or higher	14.7%	NR	CES-D–SF (≥5)	NR	Dementia (DSM-IV, n=102)
Heser *et al*, 2013 (n=2663)	Germany** (NR)	6 (NR)	81.3 (3.4)	65.3	39.0% with high school or higher	11.2%	NR	DSM-IV, GDS-15 (≥6)	NR	Dementia (DSM-IV/ ICD10, n=308) AD (DSM-IV, n=152) VaD (NINDS-AIREN, n=56)
Heun *et al*, 2006 (n=615)	Germany (NR)	4.7 (1.2)	68.1 (8.2)	59.83	NR	18.8%	NR	CIDI/DSM-IIIR	NR	AD (DSM-IIIR, n=38)
Irie *et al*, 2008 (n=1932)	USA (100% Japanese American)	6.1 (NR)	76.3 (3.6)	0	96.8% with more than 6 years of education	21.6%	NR	CES-D (11-item version; ≥9)	NR	Dementia (DSM-III-R, n=98) AD (NINCDS-ADRDA, n=NR) VaD (California AD Diagnostic and Treatment Centres criteria, n=NR)
Jessen *et al*, 2010 (n=2415)	Germany** (NR)	3 (NR)	79.5 (3.6)	64.3	34.1% with high school or higher	25.5%	45.5 (3.2) SISCO	GDS (≥6)	2.1 (2.2)	Dementia (DSM-IV, n=110) AD ((NINCDS-ADRDA, n=54) VaD (NINDS-AIREN, n=26)
Jessen *et al*, 2011 (n=1526)	Germany** (NR)	3.81 (NR)	80.1 (3.6)	65.7	36.0% with high school or higher	38.0%	NR	GDS (≥6)	NR	AD (NINCDS-ADRDA, n=88)
Jungwirth *et al*, 2009 (n=487)	Austria* (NR)	5 (NR)	75.8 (0.5)	60.9	98% with secondary school or higher	16.8%	NR	DSM-IV	NR	AD (NINCDS-ADRDA, n=30) VaD (NINDS-AIREN)

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Table 1 Continued

Author, year (number of participants)	Country (ethnic origin)	Follow-up years (SD)	Age years (SD)	Female (%)	Education, years (SD)/ level	Drop-out rate (%)	Baseline cognition score (SD)	Depression measure (cut-off)	Baseline depression score (SD)	Dementia diagnosis and criteria (number of cases)
Kim *et al*, 2010 (n=518)	South Korea†† (NR)	2.4 (0.3)	71.8 (5.1)	54.4	NR	17.1%	NR	GDS (Korean version, ≥14)	NR	Dementia (DSM-IV, n=45) AD (NINCDS-ADRDA, n=34) VaD (NINDS-AIREN, n=7)
Kim *et al*, 2011 (n=518)	South Korea†† (NR)	2.4 (0.3)	71.8 (5.1)	54.4	NR	17%	NR	Geriatric Mental State schedule (GMS)	NR	Dementia (DSM-IV, n=45) AD (NINCDS-ADRDA, n=34) VaD (NINDS-AIREN, n=7)
Kohler *et al*, 2011 (n=771)	Netherlands (NR)	9 (NR)	67.2 (7.3)	48.0	49.5% with high school or higher	11.3%	27.8 (1.8) MMSE	SCL-90 (top quartile, continuous	20.9 (6.2)	Dementia (DSM-III-R and IV, n=37) AD (NINCDS-ADRDA, n=26) VaD (NINDS-AIREN, n=11)
Lenoir *et al*, 2011 (n=7989)	France‡‡ (NR)	4 (NR)	74.0 (5.4)	61.3	23.8% with high education level	22.3%	27.4 (1.9) MMSE	CES-D (f>22, m>16)	NR	Dementia (DSM-IV, n=276) AD (NINCDS-ADRDA, n=180) VaD (NINDS-AIREN, n=24)
Li *et al*, 2011 (n=3410)	USA (NR)	7.1 (NR)	74.9 (6.2)	59.9	63.8% with college degree	8.1%	93.1 (5.0) CASI	CES-D-11 (≥11)	4.2 (4.4)	Dementia (DSM- IV, n=658) AD (NINCDS-ADRDA, n=386) VaD (NINDS-AIREN, n=89)
Luchsinger *et al*, 2008 (n=526)	USA‡ (79.5% non-white)	5.1 (3.3)	75.1 (6.4)	67.7	8.6 (4.4)	NR	NR	HAM (continuous, ≥10)	4.6 (4.4)	AD (NINCDS-ADRDA, n=114)
Luppa *et al*, 2013 (n=888)	Germany (NR)	4.3 (2.4)	81.3 (4.5)	73.4	64.3% with low education	29.8%	27.1 (1.9) MMSE	DSM-III-R CES-D (continuous, ≥23)	NR	Dementia (DSM-III-R/ IV, n=183)
Palmer *et al*, 2007 (n=185)	Sweden (NR)	3.4 (0.6)	84 (5.1)	84.9	39.2% with high school education or higher	22.4%	NR	CPRS	NR	AD (NINCDs-ADRDA, n=10)

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Table 1 Continued

Author, year (number of participants)	Country (ethnic origin)	Follow-up years (SD)	Age years (SD)	Female (%)	Education, years (SD)/ level	Drop-out rate (%)	Baseline cognition score (SD)	Depression measure (cut-off)	Baseline depression score (SD)	Dementia diagnosis and criteria (number of cases)
Palsson *et al*, 1999 (n=267)	Sweden (NR)	3 (NR)	85 (NR)	~70.8	NR	46.4%	27.9 (2.3) MMSE	DSM-III-R	NR	Dementia (DSM-III-R, n=50)
Saczynski *et al*, 2010 (n=949)	USA (NR)	8 (NR)	79.3 (5.0)	63.6	96.4% with high school or higher	NR	NR	CES-D (continuous, ≥16)	7.4 (7.5)	Dementia (DSM-IV, n=164) AD (NINCDS-ADRDA, n=136)
Samieri *et al*, 2008 (n=1214)	France‡‡ (NR)	4 (NR)	74.3 (4.9)	61.5	40.1% with high school or higher	10.9%	NR	CES-D (f>22, m>16)	7.4 (7.5)	Dementia (DSM-IV, n=65)
Schmand *et al*, 1997 (n=2114)	Netherlands¶ (NR)	4 (NR)	74.3 (5.4)	62.9	NR	41.1%	28.1 (1.5) MMSE	GMS-AGECAT	1.6 (1.1)	Dementia (GMS-AGECAT, n=131)
St John *et al*, 2002 (n=998)	Canada§ (NR)	5 (NR)	75.3 (NR)	60.2	9.9 (NR)	32.6%	89.5 (NR) 3MS	CES-D (≥16)	NR	Dementia (DSM-III-R, n=93)
van der Kommer *et al*, 2010 (n=521)	Sweden (NR)	8 (NR)	83.3 (3.0)	67.4%	29.4% with elementary school or more	47.4%	NR	CES-D (≥16)	NR	Dementia (DSM-III-R, n=93)
Vilalta-Franch *et al*, 2012 (n=451)	Spain (NR)	5 (NR)	76.9 (5.5)	65.4	4.3 (3.8)	5.09%	NR	CAMDEX, DSM-IV	NR	Dementia (DSM-IV, n=52) AD (DSM-IV, n=30) VaD (DSM-IV, n=14)
Wilson *et al*, 2003 (n=130)	USA (NR)	3.9 (NR)	81.0 (6.6)	52.3	18.1 (3.6)	<5%	NR	CES-D-SF (continuous)	NR	AD (NINCDS-ADRDA, n=51)
Wilson *et al*, 2011 (n=785)	USA (NR)	3.4 (1.4)	80.7 (7.4)	76.3	14.5 (3.1)	4.3%	28 (2.1) MMSE	NEO personality inventory revised (continuous)	11 (4.9)	AD (NINCDS-ADRD, n=94)

Studies reporting on the same cohort: *Vienna Transdanube Ageing study (VITA), †Baltimore Longitudinal Study of Aging (BLSA); ‡Washington Heights and Inwood, Columbia Aging Project, §Manitoba Study of Health and Aging (MSHA), ¶Amsterdam Study of the Elderly (AMSTEL), **Study on Aging, cognition and dementia, ††Korean prospective community survey of late-life psychiatric morbidity ‡‡Three-City Study (3C).
AD, Alzheimer's disease; CAMDEX, Cambridge Mental Disorders of the Elderly Examination; CASI, Child & Adolescent Symptom Inventory; CES-D, Centre for Epidemiological Studies Depression scale; CIDI, Composite International Diagnostic Interview; CPRS, Comprehensive Psychopathological Rating Scale; DSM, Diagnostic and Statistical Manual; GDS, Geriatric Depression Scale; GMS, Geriatric Mental State; GMS-AGECAT , Geriatric Mental State - Automated Geriatric Examination for Computer Assisted Taxonomy; HAM, Hamilton rating scale for depression; ICD, International classification of diseases; mCES-D, modified Center for Epidemiologic Studies Depression scale; MMSE, Mini-Mental State Examination; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NINDS-AIREN, National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences; NR, not reported; SCL, Symptom Checklist; VaD, vascular dementia.

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Table 2 Summary of risk estimates (HRs) for different measures of depression (continuous measures of symptomatology or categorical clinical thresholds), and different dementia outcome categories (all-cause dementia, Alzheimer's disease, vascular dementia)

	Dem				AD			
Depression assessment	**HRs (n)**	**HR**	**95% CI**	**I^2, %**	**HRs (n)**	**HR**	**95% CI**	**I^2, %**
Clinical thresholds								
All	11	1.98	1.50 to 2.63	38.34	10	2.04	1.40 to 2.98	60.28
CES-D>20	5	1.83	0.95 to 3.52	71.85	5	1.97	0.96 to 4.04	70.96
CES-D>16	9	1.69	1.46 to 1.97	0.00	6	1.58	1.25 to 2.00	0.00
Continuous measures								
All	10	1.05	1.02 to 1.08	63.06	10	1.06	1.02 to 1.10	62.06
CES-D/HAM	8	1.05	1.02 to 1.07	54.82	6	1.06	1.00 to 1.12	72.87

CES-D, Centre for Epidemiological Studies Depression scale; HAM, Hamilton rating scale for depression.

included the CES-D, HAM, GSM, and the SCL-90. In a second analysis estimates were only pooled across studies using instruments of similar range. This included the CES-D and HAM. The two sets of analyses led essentially to identical results indicating that each one point increase on the CES-D/HAM in a pooled sample with a mean age of 73.2 years (SD~6) was associated with a 5% increased risk of dementia over a mean follow-up of 5.2 years (n=8644) (see table 2 and figure 2). In addition, because the study by Devanand *et al* was the only study reporting results as RR, we conducted additional analyses excluding this study to determine whether this difference substantially influenced outcomes. These analyses showed that results remained identical when all continuous measures were considered (HR 1.05, 95% CI 1.02 to 1.08) and marginally different for CES-D/HAM measures (HR 1.04, 95% CI 1.02 to 1.07).

With respect to categorical thresholds HRs were pooled across 11 studies[21 25 27 28 30 33–36] and, as expected, risk estimates were higher for more stringent clinical criteria. A clinical diagnosis or a score greater than 20/21 on the CES-D (or equivalent) in individuals (n=15 553) in a pooled sample with a mean age of

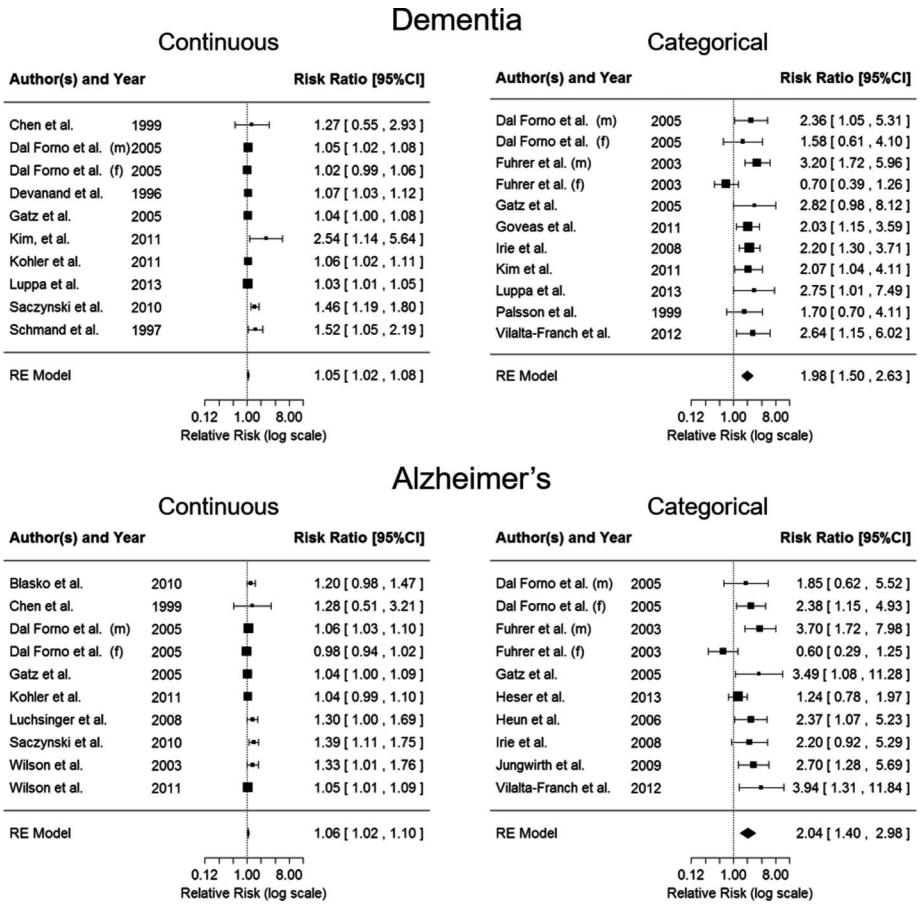

Figure 2 Forest plots of analyses investigating the risk of dementia (top row) and Alzheimer's disease (bottom row) associated with continuous (left column) and categorical (right column) depression measures including all comparable instruments.

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72.0 years (SD~6) was associated with an 83% increased risk of dementia over a mean follow-up of 8.2 years. Sensitivity analyses without the study by Fuhrer *et al* which used the equivalent validated French thresholds yielded a HR of 2.18 (95% CI 1.28 to 3.71). When a cut-off of 16[18 27 31 33 34 37–40] on the CES-D was used a 69% increased risk was observed.

Depression and AD risk

Risk estimates were first pooled across 10 studies[24 25 27 29 31 41–44] which assessed depression symptomatology as a continuous measure and a diagnosis of AD as outcome. Instruments used to assess depression included the CES-D, HAM, GDS, SCL-90 and the NEO. In a second analysis estimates were only pooled across studies using instruments of similar range. This included the CES-D and HAM.[24–27 29–31] The two sets of analyses led essentially to identical results indicating that each one point increase in a pooled sample with a mean age of 72.7 years (SD~6) on the CES-D/HAM was associated with a 6% increased risk of AD over a mean follow-up of 5.9 years (n=4401) (see table 2 and figure 2).

As in all-cause dementia analyses, pooled risk estimates for AD based on categorical depression thresholds across 10 studies[21 25 27 34 36 45–47] were higher for more stringent clinical criteria. A clinical diagnosis or a score greater than 20/21 on the CES-D (or equivalent) in individuals (n=7831) in a pooled sample with a mean age of 75.8 years (SD~5) was associated with a 97% increased risk of AD over a mean follow-up of 6.3 years. Sensitivity analyses without the study by Fuhrer *et al* which used the equivalent validated French thresholds yielded a HR of 2.43 (95% CI 1.42 to 4.16). When a cut-off of 16[27 31 34 38 39 48] on the CES-D was used a 58% increased risk was observed.

Depression and VaD risk

Very few studies provided risk estimates for VaD. Consequently, although pooled estimates were computed to provide approximate metrics to compare with risk estimates for other dementia types, they should be considered with caution. Only two studies[29 49] (n=3187; 37 VaD cases) reported on continuous measures of depressive symptomatology and produced a pooled risk estimate of 1.06 (95%CI 0.92 to 1.21). Three studies[18 34 39] (n=13 331, 113+VaD cases) reported on categorical depression thresholds that were most consistent with a CES-D threshold of 16 and produced a pooled risk estimate of 2.20 (95% CI 0.87 to 5.59).

Sensitivity analyses

For most analyses heterogeneity was low to moderate but was substantial for CES-D subanalyses using a threshold of 20. Influence of single studies was investigated with leave-one-out analyses (see online supplementary appendix SA1). In most part, they revealed no particularly influential study which could be considered outliers with some notable exceptions. The female cohort of Fuhrer *et al*[21] was found to be very influential and excluding it from the analyses for any major depression diagnosis with dementia as outcome (HR 2.29, 95% CI 1.81 to 2.88), for CES-D >20 with dementia as outcome (HR 2.56, 95% CI 1.71 to 3.84), and for CES-D >20 with AD as outcome (HR 2.79, 95% CI 1.79 to 4.33) produced notable but not significantly different estimates.

Publication bias

Publication bias was formally investigated by two methods. The fail-safe methods computes the number of studies with null findings that would be needed to reduce the significance level to α=0.05. For most analyses a large number (n=43–142) of null studies would need to be added to achieve an α level of 0.05 which suggest overall robustness to bias. Exceptions were analyses using a threshold on the CES-D of ≥20 which had a fail-safe estimate of 16 studies indicating a possible publication bias in these subanalyses. The second method used to assess publication bias was the trim-and-fill method which estimates the number of missing studies based on funnel plot asymmetry. The number of missing studies ranged from 0 to 4 representing overall about 30% (range 20–50%) of the studies included in the analyses. These results suggest that some publication bias is likely to be present and that actual effect sizes could be smaller than those reported.

Meta-regression

Influence of study quality, proportion of females, length of follow-up, and sample mean age, on pooled estimates was investigated by meta-regression on the larger analysis groups which estimated risk of all-cause dementia and AD using all compatible continuous or categorical depression measures. Some of the factors considered significantly predicted the unexplained variance in risk estimates but only in analyses including continuous measures of depression. First, when estimating the risk of all-cause dementia while considering all continuous measures of depression symptomatology, drop-out rate, female proportion, mean age and study quality accounted for 46% of unexplained variance. Studies with higher drop-out rates (β −0.2263, SE 0.0921, p=0.0140), a higher proportion of females (β −0.0077, SE 0.0021, p=0.0003), lower mean age (β 0.0115, SE 0.0039, p=0.0031), and of higher quality (β −0.0873, SE 0.0370, p=0.0182) reported on average slightly lower risk estimates. Second, when estimating the risk of AD while considering all continuous measures of depression symptomatology, female proportion and age accounted for 5% of unexplained variance. Studies with a higher proportion of females (β −0.0122, SE 0.0052, p=0.0020) and of lower mean age (β 0.0283, SE 0.0101, p=0.0052) reported on average slightly lower risk estimates.

Incompatible studies

Apart from studies which could not be pooled in specific subanalyses because they did not report on a relevant

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threshold on a specific instrument or on a specific outcome, and those which reported on the same outcomes in a single cohort,[50–55] only a single study[56] was not included in any of the analyses. This is because it was based on medical records and used ICD-9 classification to assess depression and dementia status with the possibility that particularly the latter might not reach the level of accuracy provided by methodologies used in other studies which relied on more reliable clinical criteria. However, because this study was larger than any other (n=13 535) it is important to note that the estimates it produced (dementia: HR1.77, 95% CI 1.52 to 2.06; AD: HR 2.06, 95% CI 1.67 to 2.55; VaD: HR 3.51, 95% CI 2.44 to 5.05) were remarkably consistent with the pooled estimates reported in table 1, although somewhat higher than estimates reported above for VaD but not significantly so.

DISCUSSION

The major contribution of this study was to produce precise dementia risk estimates associated with the presence of clinically significant late-life depression or depression symptomatology and which can be related to specific thresholds on validated instruments. These findings are important because evidence-based clinical practice mandates that clinical advice and decision-making be based on objective measures of risk. Until now, this evidence was not available for specific instruments at specified thresholds.

Great care was taken to avoid the combination of incompatible findings. As such we were not only able to confirm that depression is associated with increased risk of dementia but also to provide summary estimates showing that this association is very similar for all-cause dementia and AD. Importantly detailed analyses at specific cut-offs further confirmed this pattern of association. Of particular relevance to clinicians and researchers, separate analyses of studies using a cut-off most consistent with major depression and previously validated against clinical criteria (CED-D>20)[57] demonstrated somewhat higher risk estimates (dementia HR 1.83 (trend) and AD HR 1.97) than those using a more lenient cut-off (CES-D>16; dementia HR 1.58 (trend) and AD HR 1.69). Together these findings suggest that clinical depression is likely associated with an approximately 80–100% increased risk of dementia and AD. However, milder presentation is still associated with an approximately 60–70% increased risk of dementia and AD. In this context it is noteworthy that Coopers *et al*[58] found, when considering risk of transition from MCI to dementia, that depression was associated with an increased risk when focusing on population studies but not when investigating clinical studies. The reason for these findings remains to be elucidated. However, it is possible that depression is most predictive of dementia risk in the early, preclinical stages of the disease and that in individuals involved in clinical studies who are likely to be in more advanced stages of the disease, depression is a less sensitive predictor.

Analyses of continuous measures with a similar range (CES-D, HAM and SCL-90) or from the CES-D alone also suggest depression may be associated with dementia in a dose-dependent manner and possibly starting in the subclinical range. Indeed, every one point increase on these measures was associated with a 5–6% increased risk of AD or dementia. The available data do not allow us to investigate whether the demonstrated association is driven by a stronger dose-dependent effect within the clinical population or whether a smaller effect is at play across the whole subclinical and clinical ranges. This question should be addressed in future research as it will lead to more reliable risk estimates and will help clarify the extent to which those with subsyndromal symptomatology are at risk.

Too few studies were available to produce reliable risk estimates for VaD. However, despite this major limitation, summary HRs for VaD were very consistent with those produced for all-cause dementia and AD, and did not significantly differ (as demonstrated by the predominantly overlapping CIs). Together these findings suggest that the risk associated with depression does not differ for the main types of dementia considered here.

Interestingly, meta-regression analyses showed that higher drop-out rate, larger female proportion, younger mean age and higher study quality ratings were associated with lower dementia and AD risk estimates but only when continuous depression measures were considered. These findings further emphasise the need for very robust methodology in epidemiological research based on designs that minimise drop-out, do not cover excessively large age ranges (or stratify by age groups), include similar proportions of males and females (or stratify by sex), and that adhere and report high scientific quality practices. It is also particularly notable that according to our meta-regression analysis late-life depression in women appeared to be associated with a slightly lower risk.

An incompletely resolved question is whether depression is a risk factor for dementia or whether it is an early biomarker which indicates the development of depressive symptomatology in the prodromal stages of the disease. Indeed, while all studies included in the present investigation excluded individuals presenting with dementia at baseline, at least in those studies with short follow-ups it could be argued that participants might have already have developed mild cognitive impairment and/or substantial cerebral pathology. While this may be in part the case it is also unlikely that depression is only a symptom of dementia and not a risk for it. This is because even studies with long follow-ups (eg, more than 20 years in Dotson *et al*[37]) have found a significant risk of dementia associated with depression but perhaps even more convincing is the profuse evidence demonstrating links between the development of depression and increased neuroinflammation, oxidative

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stress, white matter lesions and cerebral atrophy which are already detectable in younger cohorts (see ref. [59] for a review and discussion).

Major strengths of this study were that it used a robust methodology which included a very broad search of the literature using clearly defined search terms and stringent inclusion and exclusion criteria. Particular care was taken to assess study characteristics so only studies which used compatible exposure and outcome measures would be combined. Detailed subanalyses were conducted to provide estimates for specific tools at specific thresholds. Moreover, study quality, publication bias, and influence of relevant factors were formally investigated by meta-regression. However, the study was limited by the relatively small number of articles with relevant data published in this domain and particularly so for VaD. Estimated HRs had relatively wide CIs which suggest that further research is required to produce even more precise estimates. The fact that the CES-D was the only instrument that could be analysed separately was also a limitation. Another limitation stems from the fact that different studies did not control for exactly the same covariates which may have somewhat biased estimates.

In conclusion, when considering specific screening instruments at specified threshold, late-life depression and depressive symptomatology are consistently associated with an increased risk of dementia and AD. The CES-D is the only psychometric instrument for which specific risk estimates could be computed at known validated thresholds (16 and 20). More research needs to be conducted to determine the extent to which depressive symptomatology in the subclinical range is associated with increased dementia risk. While this study could only demonstrate associations and not causal links, available evidence support the view that depressive symptomatology is associated with pathological mechanisms associated with neurodegeneration.[59] Therefore, preventative approaches to reduce the prevalence and virulence of depressive illness need to be further developed as, in addition to personal costs, it will be associated with exponential social and economic costs in our ageing population.

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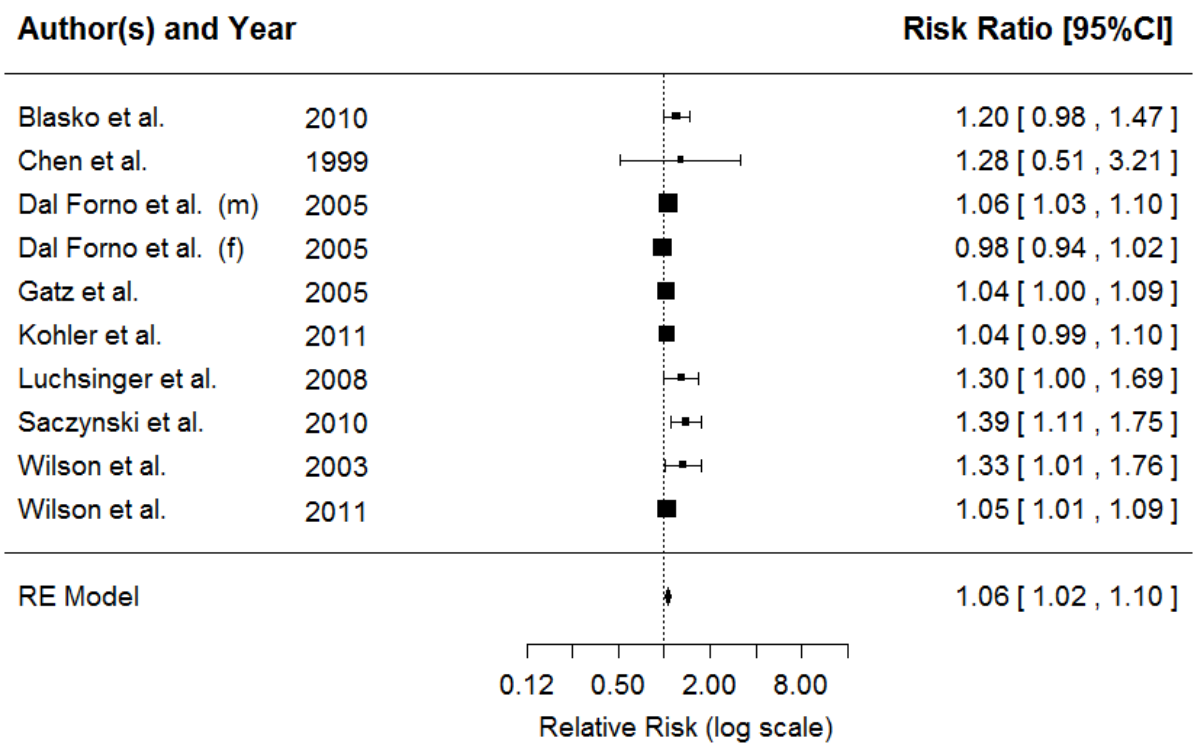
Appendix SA1 (analyses details):

AD continuous (all compatible)



Random-Effects Model (k = 10; tau^2 estimator: DL)

```
 logLik  deviance      AIC      BIC     AICc
 8.1673   22.1823  -12.3346  -11.7294  -10.6203

tau^2 (estimated amount of total heterogeneity): 0.0015 (SE = 0.0014)
tau (square root of estimated tau^2 value):      0.0391
I^2 (total heterogeneity / total variability):   62.06%
H^2 (total variability / sampling variability):  2.64

Test for Heterogeneity:
Q(df = 9) = 23.7240, p-val = 0.0048

Model Results:

estimate      se     zval     pval    ci.lb    ci.ub
  0.0536   0.0190   2.8217   0.0048   0.0164   0.0908      **

---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.0492	0.0189	2.5979	0.0094	0.0121	0.0863	21.8313	0.0052	0.0015	63.3553	2.7289

2	0.054	0.0194	2.7833	0.0054	0.016	0.0919	23.53	0.0027	0.0016	66.0008	2.9412
3	0.0586	0.024	2.437	0.0148	0.0115	0.1057	22.1508	0.0046	0.0022	63.8839	2.7688
4	0.0623	0.0165	3.7839	0.0002	0.0301	0.0946	13.2307	0.1042	0.0007	39.5346	1.6538
5	0.0619	0.0235	2.6365	0.0084	0.0159	0.108	23.7195	0.0026	0.0021	66.2725	2.9649
6	0.0601	0.0226	2.6605	0.0078	0.0158	0.1044	23.7212	0.0026	0.0019	66.2749	2.9651
7	0.0486	0.0184	2.6442	0.0082	0.0126	0.0847	21.0271	0.0071	0.0014	61.9539	2.6284
8	0.0438	0.0166	2.6455	0.0082	0.0114	0.0763	17.505	0.0253	0.001	54.2989	2.1881
9	0.0484	0.0182	2.6532	0.008	0.0126	0.0841	20.7307	0.0079	0.0013	61.4098	2.5913
10	0.061	0.0241	2.5344	0.0113	0.0138	0.1081	23.4956	0.0028	0.0022	65.951	2.9369

Fail-safe N Calculation Using the Rosenthal Approach

Fail-safe N Calculation Using the Rosenthal Approach
Observed Significance Level: <.0001
Target Significance Level: 0.05
Fail-safe N: 101

Trim-and-fill analysis

Estimated number of missing studies on the left side: 5 (SE = 1.9266)

Random-Effects Model (k = 15; tau^2 estimator: DL)

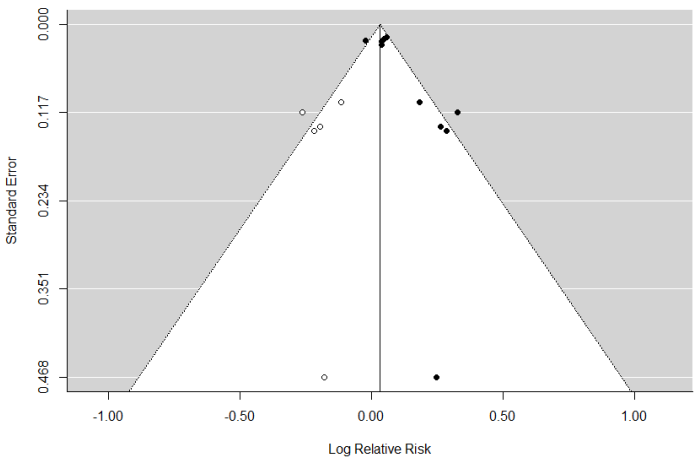
tau^2 (estimated amount of total heterogeneity): 0.0025 (SE = 0.0021)
tau (square root of estimated tau^2 value): 0.0501
I^2 (total heterogeneity / total variability): 64.10%
H^2 (total variability / sampling variability): 2.79

Test for Heterogeneity:
Q(df = 14) = 38.9936, p-val = 0.0004

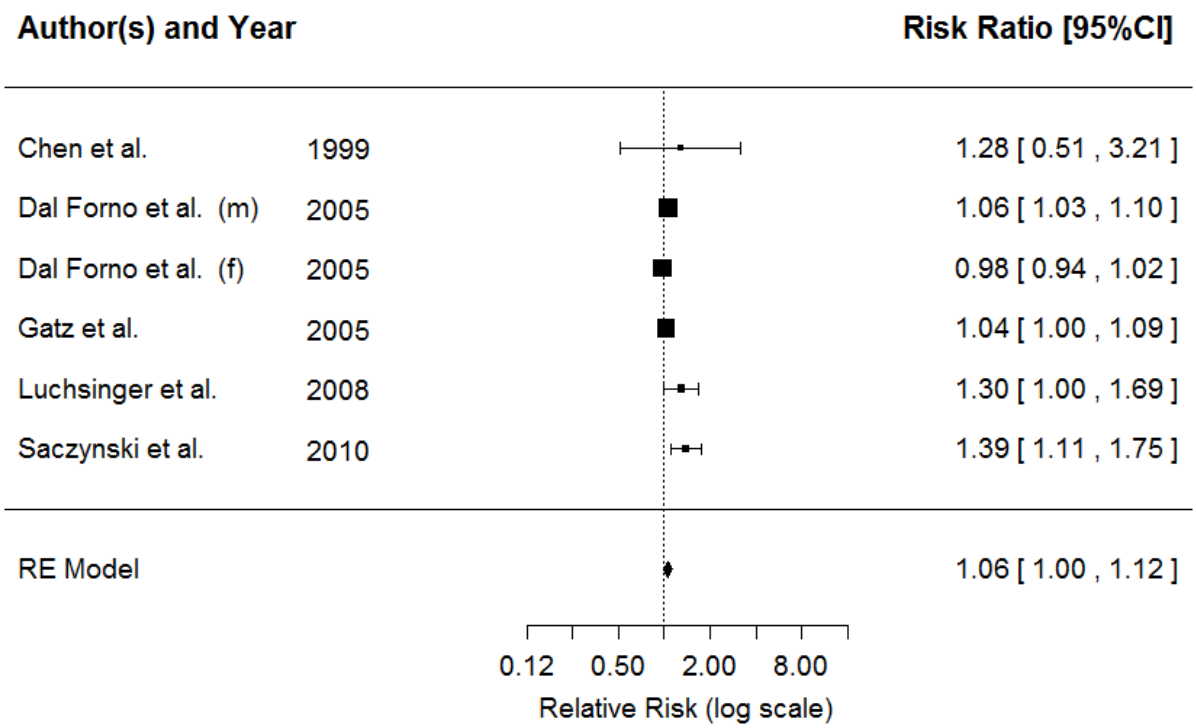
Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
0.0334	0.0215	1.5493	0.1213	-0.0088	0.0756

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1



AD continuous (CES-D/HAM)



Random-Effects Model (k = 7; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
3.5299	15.2687	-3.0598	-3.4762	0.9402

tau^2 (estimated amount of total heterogeneity): 0.0025 (SE = 0.0029)
tau (square root of estimated tau^2 value): 0.0505
I^2 (total heterogeneity / total variability): 72.87%
H^2 (total variability / sampling variability): 3.69

Test for Heterogeneity:
Q(df = 5) = 18.4272, p-val = 0.0025

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.0538	0.0297	1.8108	0.0702	-0.0044	0.1121	.

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.0661	0.0314	2.1066	0.0352	0.0046	0.1275	21.3265	0.0007	0.0031	76.555	4.2653
2	0.0928	0.0462	2.0118	0.0442	0.0024	0.1833	18.5071	0.0024	0.0056	72.9833	3.7014
3	0.0911	0.0325	2.8064	0.005	0.0275	0.1548	11.1795	0.0479	0.0022	55.2754	2.2359
4	0.0977	0.0453	2.1576	0.031	0.009	0.1865	21.5077	0.0006	0.0054	76.7525	4.3015

5	0.0544	0.03	1.8121	0.07	-0.0044	0.1133	18.7243	0.0022	0.0026	73.2967	3.7449
6	0.044	0.0269	1.6383	0.1014	-0.0086	0.0966	15.1112	0.0099	0.0019	66.9119	3.0222
7	0.0538	0.0297	1.8108	0.0702	-0.0044	0.1121	18.4272	0.0025	0.0025	72.8661	3.6854

Fail-safe N Calculation Using the Rosenthal Approach

Observed Significance Level: <.0001
Target Significance Level: 0.05
Fail-safe N: 43

Trim-and-fill analysis

Estimated number of missing studies on the left side: 3 (SE = 1.6850)

Random-Effects Model (k = 10; tau^2 estimator: DL)

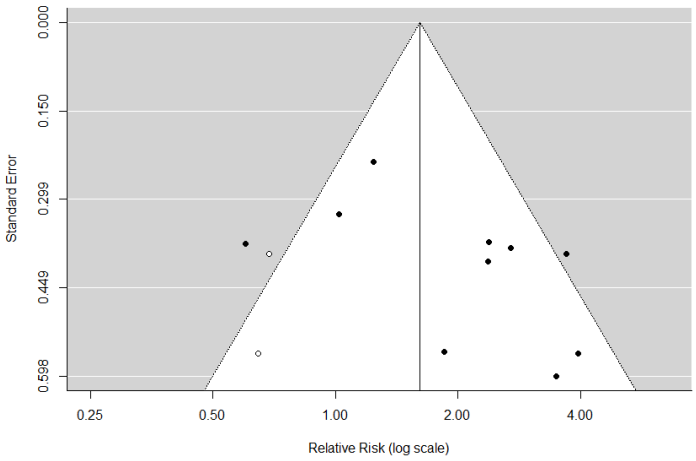
tau^2 (estimated amount of total heterogeneity): 0.0047 (SE = 0.0048)
tau (square root of estimated tau^2 value): 0.0686
I^2 (total heterogeneity / total variability): 74.45%
H^2 (total variability / sampling variability): 3.91

Test for Heterogeneity:
Q(df = 9) = 35.2272, p-val < .0001

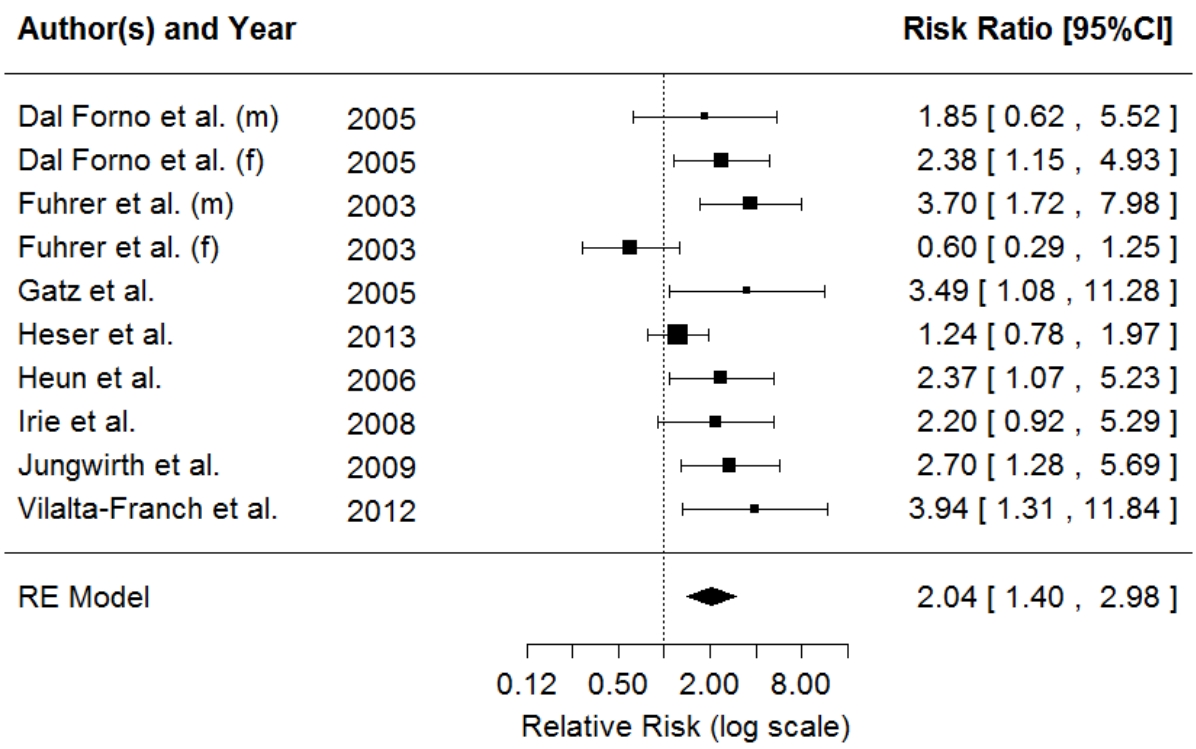
Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
0.0276	0.0339	0.8125	0.4165	-0.0389	0.0940

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1



AD Clinical Threshold (All compatible)



Random-Effects Model (k = 10; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
-8.5049	16.0360	21.0097	21.6149	22.7240

tau^2 (estimated amount of total heterogeneity): 0.1929 (SE = 0.1725)
tau (square root of estimated tau^2 value): 0.4392
I^2 (total heterogeneity / total variability): 54.92%
H^2 (total variability / sampling variability): 2.22

Test for Heterogeneity:
Q(df = 9) = 19.9626, p-val = 0.0181

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.7138	0.1924	3.7096	0.0002	0.3367	1.0910	***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.0492	0.0189	2.5979	0.0094	0.0121	0.0863	21.8313	0.0052	0.0015	63.3553	2.7289
2	0.054	0.0194	2.7833	0.0054	0.016	0.0919	23.53	0.0027	0.0016	66.0008	2.9412
3	0.0586	0.024	2.437	0.0148	0.0115	0.1057	22.1508	0.0046	0.0022	63.8839	2.7688
4	0.0623	0.0165	3.7839	0.0002	0.0301	0.0946	13.2307	0.1042	0.0007	39.5346	1.6538
5	0.0619	0.0235	2.6365	0.0084	0.0159	0.108	23.7195	0.0026	0.0021	66.2725	2.9649
6	0.0601	0.0226	2.6605	0.0078	0.0158	0.1044	23.7212	0.0026	0.0019	66.2749	2.9651

7	0.0486	0.0184	2.6442	0.0082	0.0126	0.0847	21.0271	0.0071	0.0014	61.9539	2.6284
8	0.0438	0.0166	2.6455	0.0082	0.0114	0.0763	17.505	0.0253	0.001	54.2989	2.1881
9	0.0484	0.0182	2.6532	0.008	0.0126	0.0841	20.7307	0.0079	0.0013	61.4098	2.5913
10	0.061	0.0241	2.5344	0.0113	0.0138	0.1081	23.4956	0.0028	0.0022	65.951	2.9369

Fail-safe N Calculation Using the Rosenthal Approach

Observed Significance Level: <.0001
Target Significance Level: 0.05
Fail-safe N: 102

Trim-and-fill analysis

Estimated number of missing studies on the left side: 3 (SE = 2.1498)

Random-Effects Model (k = 13; tau^2 estimator: DL)

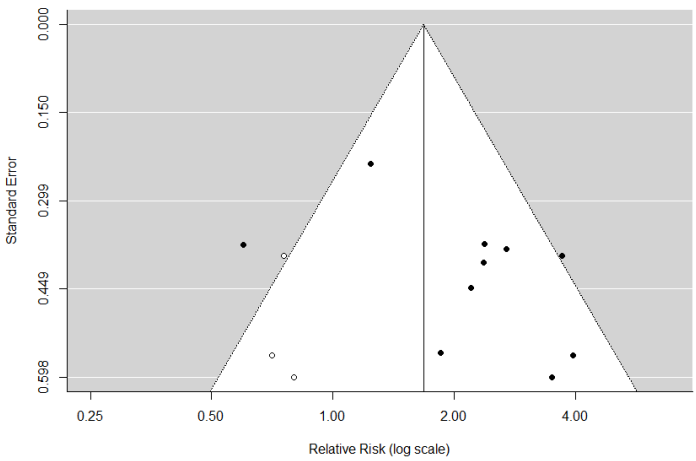
tau^2 (estimated amount of total heterogeneity): 0.2369 (SE = 0.1753)
tau (square root of estimated tau^2 value): 0.4867
I^2 (total heterogeneity / total variability): 58.01%
H^2 (total variability / sampling variability): 2.38

Test for Heterogeneity:
Q(df = 12) = 28.5795, p-val = 0.0045

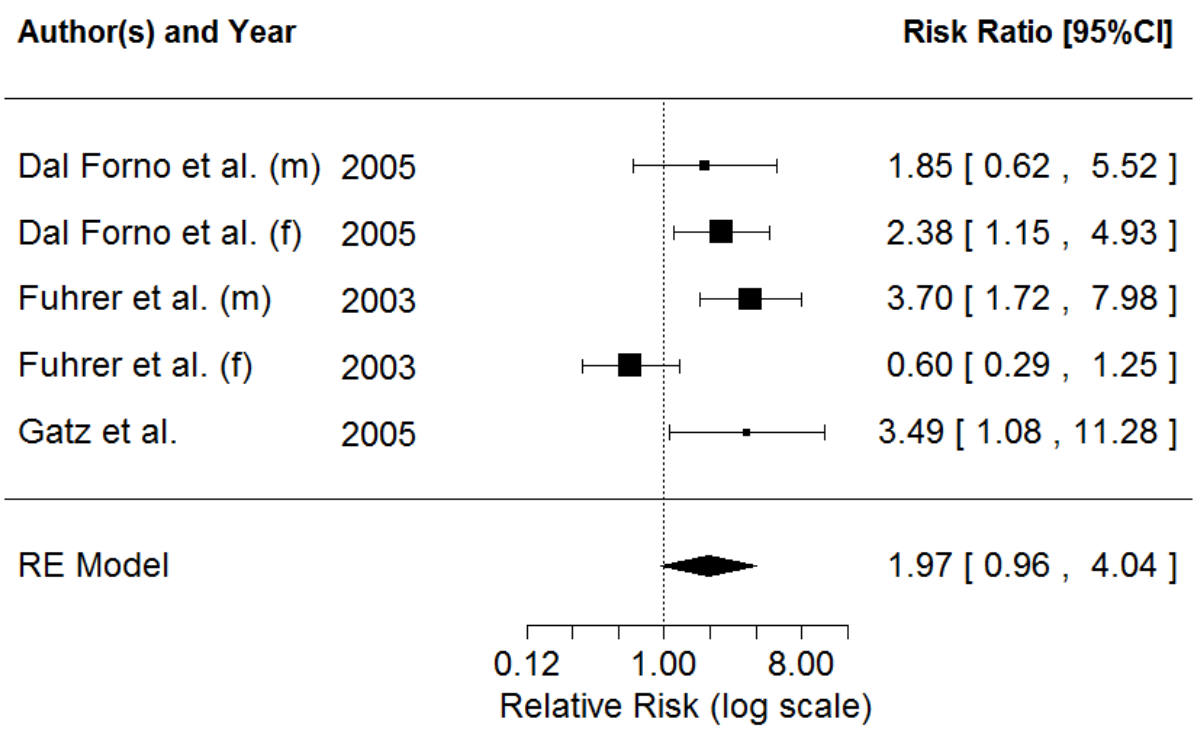
Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.5181	0.1823	2.8415	0.0045	0.1607	0.8755	**

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’



AD Clinical Threshold (CES-D > 20)



Random-Effects Model (k = 5; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
-5.3513	9.5265	14.7026	13.9215	20.7026

tau^2 (estimated amount of total heterogeneity): 0.4698 (SE = 0.4821)
tau (square root of estimated tau^2 value): 0.6854
I^2 (total heterogeneity / total variability): 70.96%
H^2 (total variability / sampling variability): 3.44

Test for Heterogeneity:
Q(df = 4) = 13.7733, p-val = 0.0081

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.6757	0.3682	1.8351	0.0665	-0.0460	1.3973	.

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.6953	0.4513	1.5407	0.1234	-0.1892	1.5798	13.7733	0.0032	0.6264	78.2188	4.5911
2	0.6327	0.4892	1.2933	0.1959	-0.3262	1.5915	13.1567	0.0043	0.726	77.1979	4.3856
3	0.4993	0.414	1.2061	0.2278	-0.3121	1.3107	9.6725	0.0216	0.4626	68.9843	3.2242
4	1.0257	0.225	4.5583	0	0.5847	1.4667	1.3841	0.7093	0	0	1
5	0.5639	0.4242	1.3295	0.1837	-0.2674	1.3952	12.527	0.0058	0.5404	76.0517	4.1757

Fail-safe N Calculation Using the Rosenthal Approach

Observed Significance Level: 0.0004
Target Significance Level: 0.05

Fail-safe N: 16

Trim-and-fill analysis

Estimated number of missing studies on the left side: 1 (SE = 1.7009)

Random-Effects Model (k = 6; tau^2 estimator: DL)

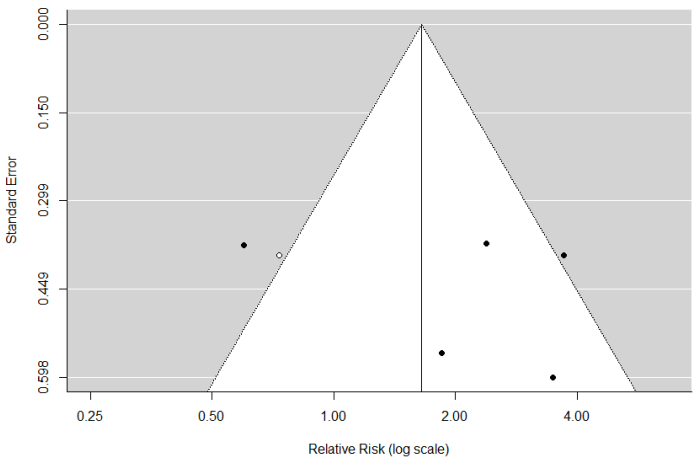
tau^2 (estimated amount of total heterogeneity): 0.4876 (SE = 0.4359)
tau (square root of estimated tau^2 value): 0.6983
I^2 (total heterogeneity / total variability): 72.65%
H^2 (total variability / sampling variability): 3.66

Test for Heterogeneity:
Q(df = 5) = 18.2798, p-val = 0.0026

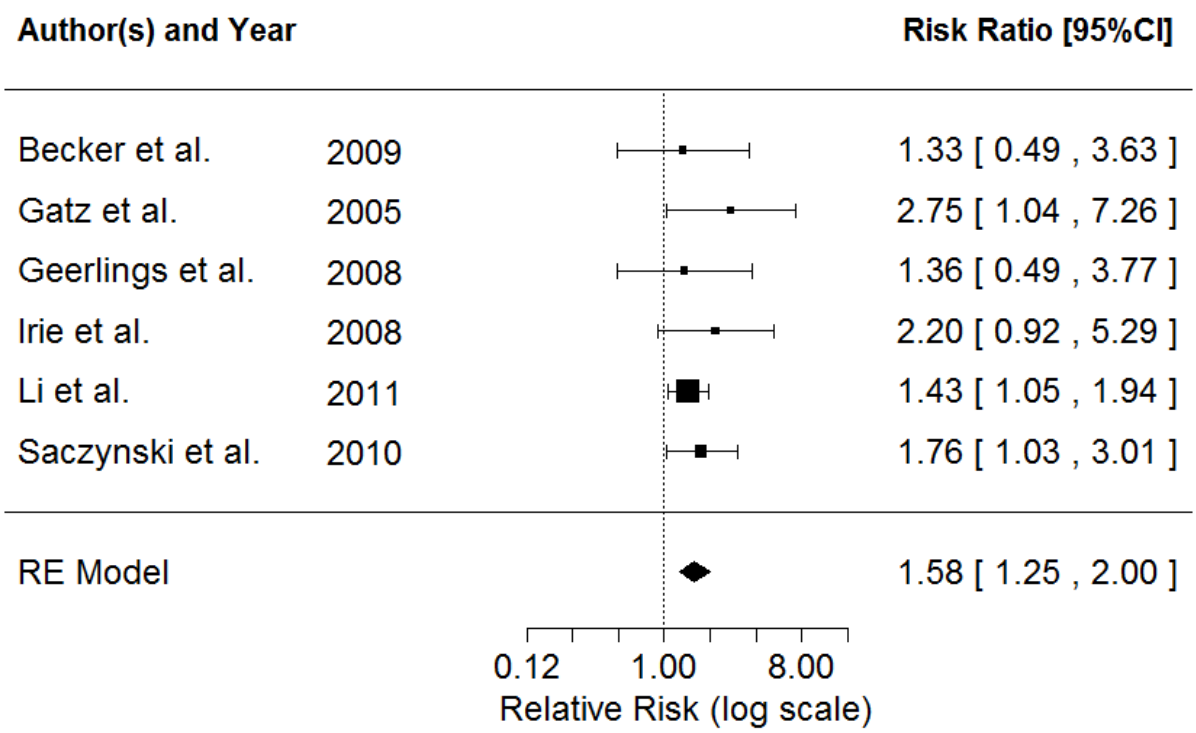
Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
0.5005	0.3382	1.4801	0.1389	-0.1623	1.1633

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1



AD Clinical Threshold (CES-D > 16)



Random-Effects Model (k = 6; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
-0.8119	2.5581	5.6239	5.2074	9.6239

tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.0724)
tau (square root of estimated tau^2 value): 0
I^2 (total heterogeneity / total variability): 0.00%
H^2 (total variability / sampling variability): 1.00

Test for Heterogeneity:
Q(df = 5) = 2.5581, p-val = 0.7677

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.4585	0.1189	3.8561	0.0001	0.2255	0.6916	***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.5958	0.1827	3.2608	0.0011	0.2377	0.954	1.5787	0.8126	0	0	1
2	0.4684	0.1222	3.8315	0.0001	0.2288	0.708	2.4371	0.6559	0	0	1
3	0.4247	0.1225	3.4667	0.0005	0.1846	0.6648	1.2333	0.8726	0	0	1
4	0.4669	0.1221	3.8221	0.0001	0.2275	0.7063	2.469	0.6502	0	0	1
5	0.4335	0.1233	3.5142	0.0004	0.1917	0.6752	1.9731	0.7407	0	0	1
6	0.4337	0.132	3.2844	0.001	0.1749	0.6924	2.3703	0.668	0	0	1

Fail-safe N Calculation Using the Rosenthal Approach

Fail-safe N Calculation Using the Rosenthal Approach
Observed Significance Level: <.0001
Target Significance Level: 0.05
Fail-safe N: 26

Estimated number of missing studies on the left side: 0 (SE = 1.6829)

Estimated number of missing studies on the left side: 2 (SE = 1.7837)

Random-Effects Model (k = 8; tau^2 estimator: DL)

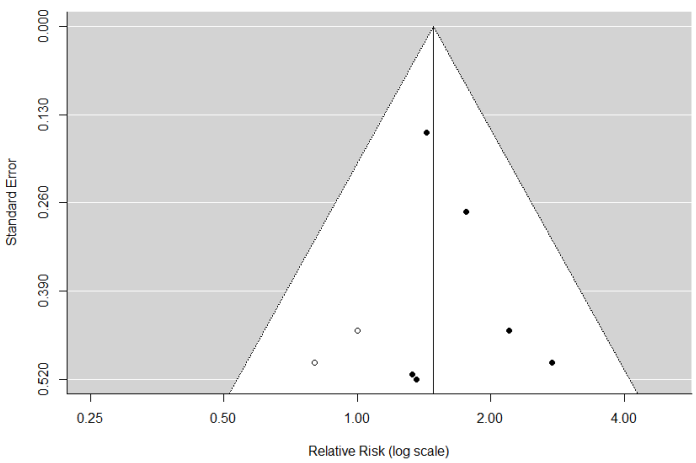
tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.0676)
tau (square root of estimated tau^2 value): 0
I^2 (total heterogeneity / total variability): 0.00%
H^2 (total variability / sampling variability): 1.00

Test for Heterogeneity:
Q(df = 7) = 5.1651, p-val = 0.6398

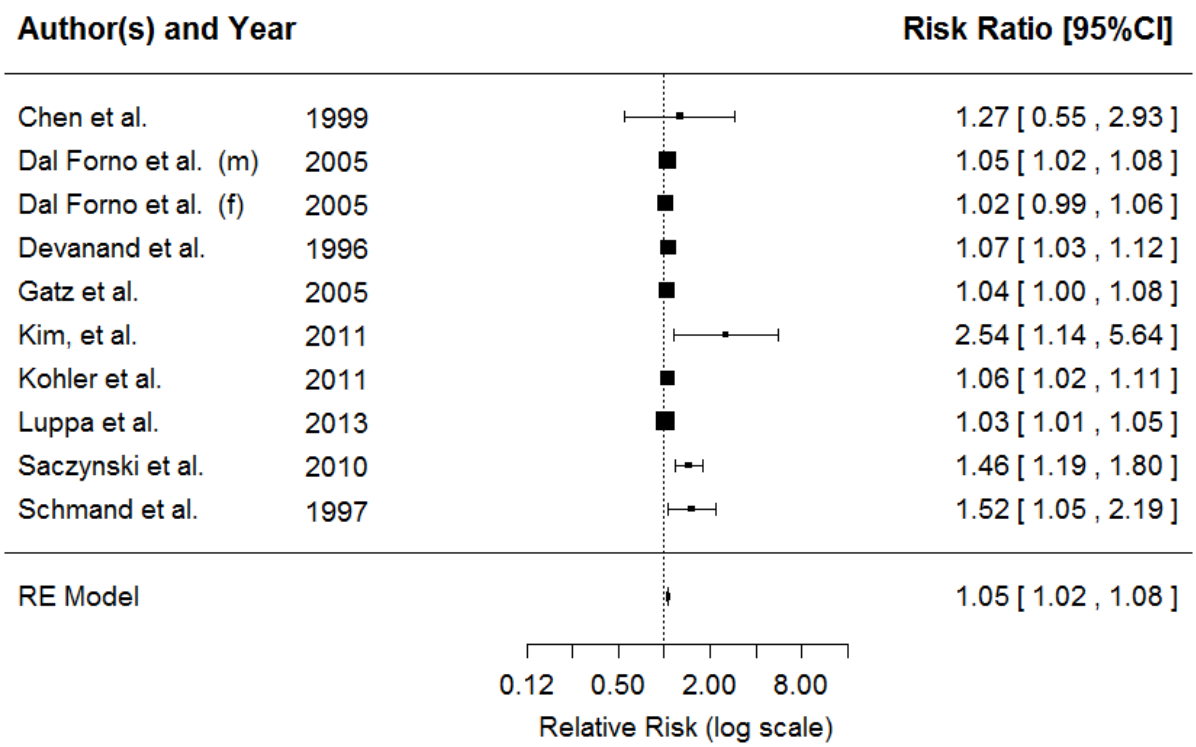
Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.3952	0.1119	3.5302	0.0004	0.1758	0.6146	***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1



Dementia continuous (all compatible)



Random-Effects Model (k = 10; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
7.1882	27.5279	-10.3764	-9.7712	-8.6621

tau^2 (estimated amount of total heterogeneity): 0.0008 (SE = 0.0007)
tau (square root of estimated tau^2 value): 0.0284
I^2 (total heterogeneity / total variability): 63.06%
H^2 (total variability / sampling variability): 2.71

Test for Heterogeneity:
Q(df = 9) = 24.3653, p-val = 0.0038

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.0508	0.0135	3.7672	0.0002	0.0244	0.0772	***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.0492	0.0189	2.5979	0.0094	0.0121	0.0863	21.8313	0.0052	0.0015	63.3553	2.7289
2	0.054	0.0194	2.7833	0.0054	0.016	0.0919	23.53	0.0027	0.0016	66.0008	2.9412
3	0.0586	0.024	2.437	0.0148	0.0115	0.1057	22.1508	0.0046	0.0022	63.8839	2.7688
4	0.0623	0.0165	3.7839	0.0002	0.0301	0.0946	13.2307	0.1042	0.0007	39.5346	1.6538
5	0.0619	0.0235	2.6365	0.0084	0.0159	0.108	23.7195	0.0026	0.0021	66.2725	2.9649
6	0.0601	0.0226	2.6605	0.0078	0.0158	0.1044	23.7212	0.0026	0.0019	66.2749	2.9651
7	0.0486	0.0184	2.6442	0.0082	0.0126	0.0847	21.0271	0.0071	0.0014	61.9539	2.6284

8	0.0438	0.0166	2.6455	0.0082	0.0114	0.0763	17.505	0.0253	0.001	54.2989	2.1881
9	0.0484	0.0182	2.6532	0.008	0.0126	0.0841	20.7307	0.0079	0.0013	61.4098	2.5913
10	0.061	0.0241	2.5344	0.0113	0.0138	0.1081	23.4956	0.0028	0.0022	65.951	2.9369

Fail-safe N Calculation Using the Rosenthal Approach

Observed Significance Level: <.0001
Target Significance Level: 0.05
Fail-safe N: 121

Trim-and-fill analysis

Estimated number of missing studies on the left side: 3 (SE = 2.3645)

Random-Effects Model (k = 15; tau^2 estimator: DL)

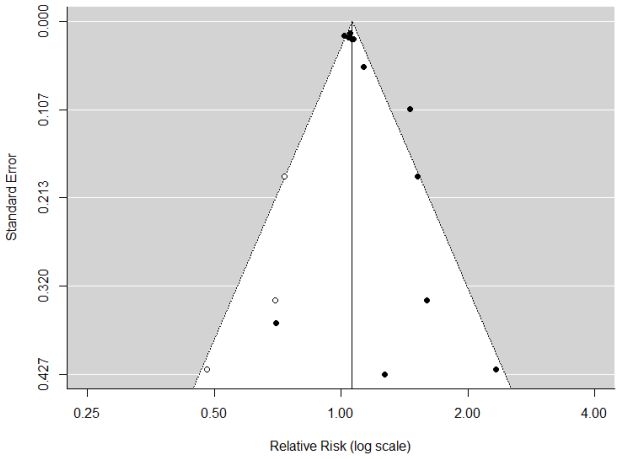
tau^2 (estimated amount of total heterogeneity): 0.0017 (SE = 0.0015)
tau (square root of estimated tau^2 value): 0.0409
I^2 (total heterogeneity / total variability): 59.23%
H^2 (total variability / sampling variability): 2.45

Test for Heterogeneity:
Q(df = 14) = 34.3394, p-val = 0.0018

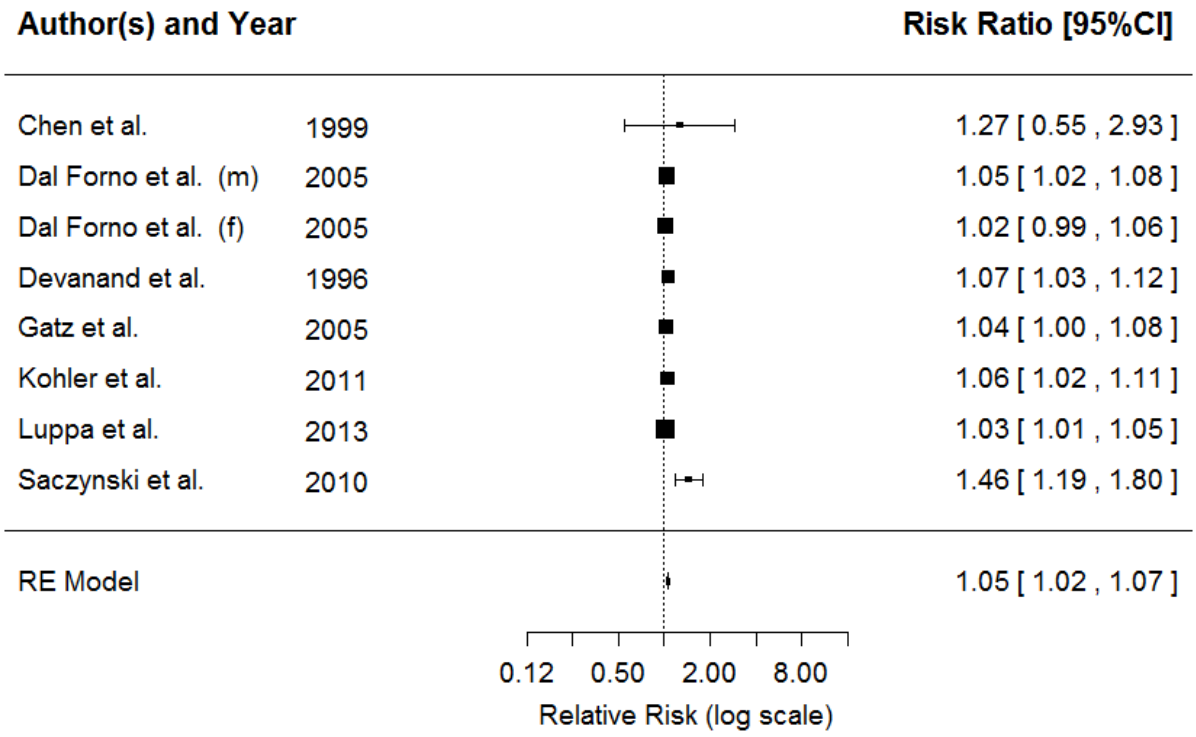
Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.0606	0.0188	3.2296	0.0012	0.0238	0.0974	**

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1



Dementia continuous (CES-D/HAM)



Random-Effects Model (k = 8; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
11.3939	17.6476	-18.7878	-18.6290	-16.3878

tau^2 (estimated amount of total heterogeneity): 0.0004 (SE = 0.0005)
tau (square root of estimated tau^2 value): 0.0211
I^2 (total heterogeneity / total variability): 54.82%
H^2 (total variability / sampling variability): 2.21

Test for Heterogeneity:
Q(df = 7) = 15.4937, p-val = 0.0302

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.0457	0.0111	4.1261	<.0001	0.0240	0.0674	***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.0492	0.0189	2.5979	0.0094	0.0121	0.0863	21.8313	0.0052	0.0015	63.3553	2.7289
2	0.054	0.0194	2.7833	0.0054	0.016	0.0919	23.53	0.0027	0.0016	66.0008	2.9412
3	0.0586	0.024	2.437	0.0148	0.0115	0.1057	22.1508	0.0046	0.0022	63.8839	2.7688
4	0.0623	0.0165	3.7839	0.0002	0.0301	0.0946	13.2307	0.1042	0.0007	39.5346	1.6538
5	0.0619	0.0235	2.6365	0.0084	0.0159	0.108	23.7195	0.0026	0.0021	66.2725	2.9649
6	0.0601	0.0226	2.6605	0.0078	0.0158	0.1044	23.7212	0.0026	0.0019	66.2749	2.9651
7	0.0486	0.0184	2.6442	0.0082	0.0126	0.0847	21.0271	0.0071	0.0014	61.9539	2.6284

8	0.0438	0.0166	2.6455	0.0082	0.0114	0.0763	17.505	0.0253	0.001	54.2989	2.1881
9	0.0484	0.0182	2.6532	0.008	0.0126	0.0841	20.7307	0.0079	0.0013	61.4098	2.5913
10	0.061	0.0241	2.5344	0.0113	0.0138	0.1081	23.4956	0.0028	0.0022	65.951	2.9369

Fail-safe N Calculation Using the Rosenthal Approach

Observed Significance Level: <.0001
Target Significance Level: 0.05
Fail-safe N: 131

Trim-and-fill analysis

Estimated number of missing studies on the left side: 3 (SE = 1.8667)

Random-Effects Model (k = 11; tau^2 estimator: DL)

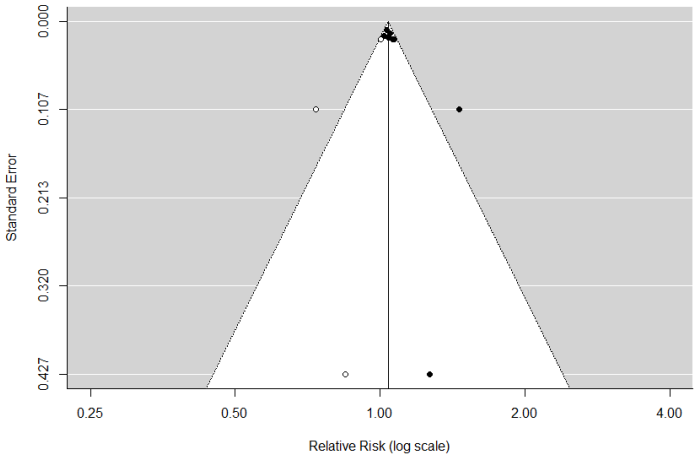
tau^2 (estimated amount of total heterogeneity): 0.0009 (SE = 0.0007)
tau (square root of estimated tau^2 value): 0.0294
I^2 (total heterogeneity / total variability): 65.12%
H^2 (total variability / sampling variability): 2.87

Test for Heterogeneity:
Q(df = 10) = 28.6690, p-val = 0.0014

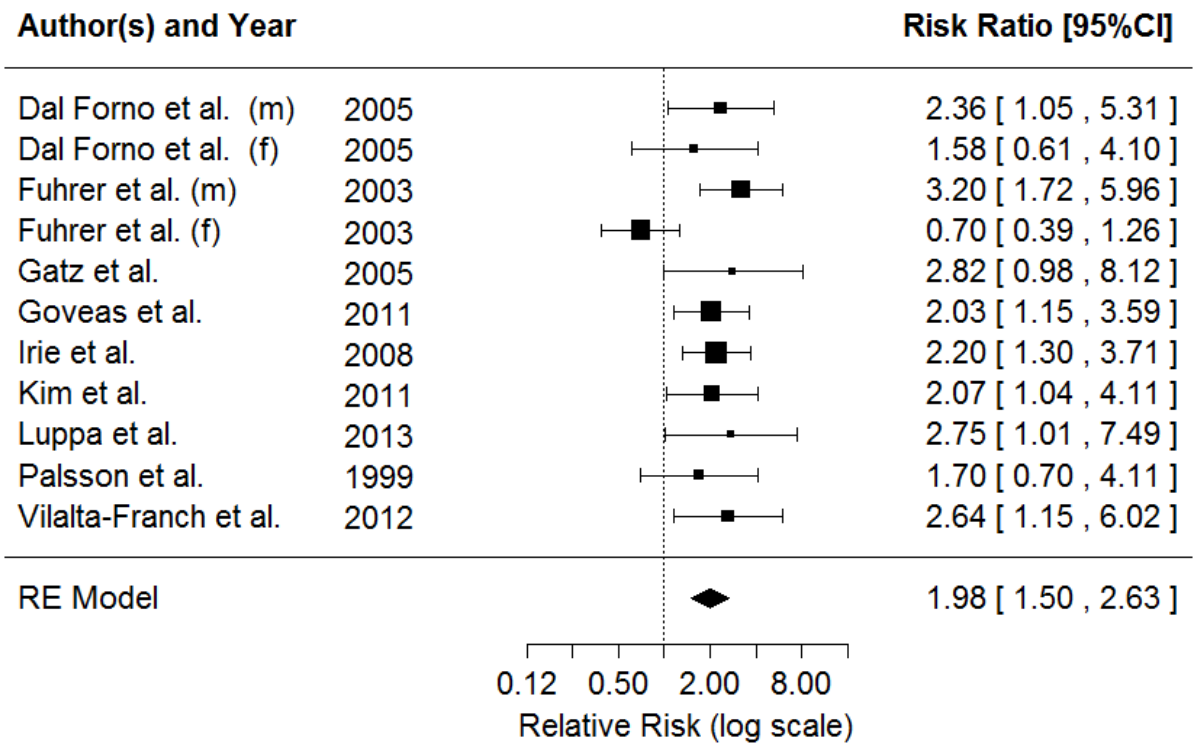
Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.0377	0.0129	2.9318	0.0034	0.0125	0.0629	**

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1



Dementia categorical (All compatible)



Random-Effects Model (k = 9; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
-6.6395	14.0693	17.2790	18.0748	18.7790

tau^2 (estimated amount of total heterogeneity): 0.0844 (SE = 0.0998)
tau (square root of estimated tau^2 value): 0.2905
I^2 (total heterogeneity / total variability): 38.34%
H^2 (total variability / sampling variability): 1.62

Test for Heterogeneity:
Q(df = 10) = 16.2182, p-val = 0.0936

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.6855	0.1441	4.7573	<.0001	0.4031	0.9679	***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.6725	0.157	4.2824	0	0.3647	0.9803	15.9913	0.0671	0.1034	43.7193	1.7768
2	0.704	0.155	4.5409	0	0.4001	1.0078	16.0193	0.0665	0.1014	43.8178	1.7799
3	0.6222	0.1476	4.2152	0	0.3329	0.9116	13.46	0.1429	0.0698	33.135	1.4956
4	0.8265	0.118	7.0026	0	0.5952	1.0579	2.8003	0.9717	0	0	1
5	0.666	0.1524	4.3692	0	0.3672	0.9648	15.7327	0.0727	0.0962	42.7944	1.7481
6	0.6865	0.1643	4.1774	0	0.3644	1.0087	16.1967	0.0629	0.1155	44.4332	1.7996
7	0.6745	0.165	4.0876	0	0.3511	0.9979	15.975	0.0674	0.115	43.662	1.775

8	0.6842	0.1607	4.2566	0	0.3691	0.9992	16.1867	0.0631	0.1098	44.3989	1.7985
9	0.6659	0.1531	4.3498	0	0.3658	0.9659	15.7466	0.0724	0.0969	42.8446	1.7496
10	0.7004	0.1565	4.4761	0	0.3937	1.0071	16.1187	0.0644	0.1039	44.1642	1.791
11	0.6627	0.1551	4.2715	0	0.3586	0.9668	15.6741	0.074	0.0984	42.5805	1.7416

Fail-safe N Calculation Using the Rosenthal Approach

Observed Significance Level: <.0001
Target Significance Level: 0.05
Fail-safe N: 142

Trim-and-fill analysis

Estimated number of missing studies on the left side: 4 (SE = 2.1937)

Random-Effects Model (k = 15; tau^2 estimator: DL)

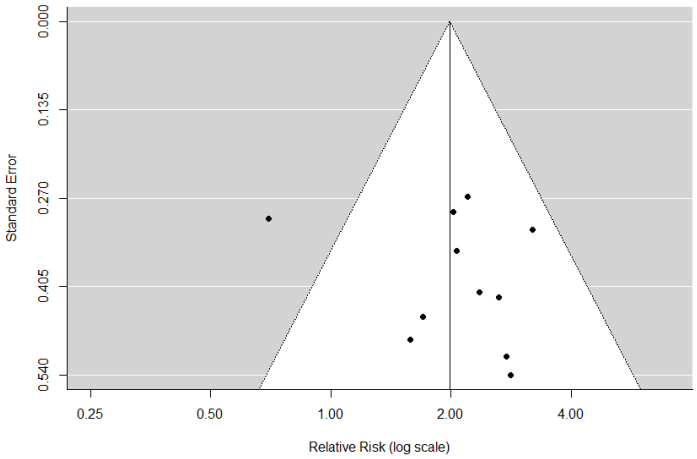
tau^2 (estimated amount of total heterogeneity): 0.1145 (SE = 0.0999)
tau (square root of estimated tau^2 value): 0.3384
I^2 (total heterogeneity / total variability): 44.24%
H^2 (total variability / sampling variability): 1.79

Test for Heterogeneity:
Q(df = 14) = 25.1089, p-val = 0.0335

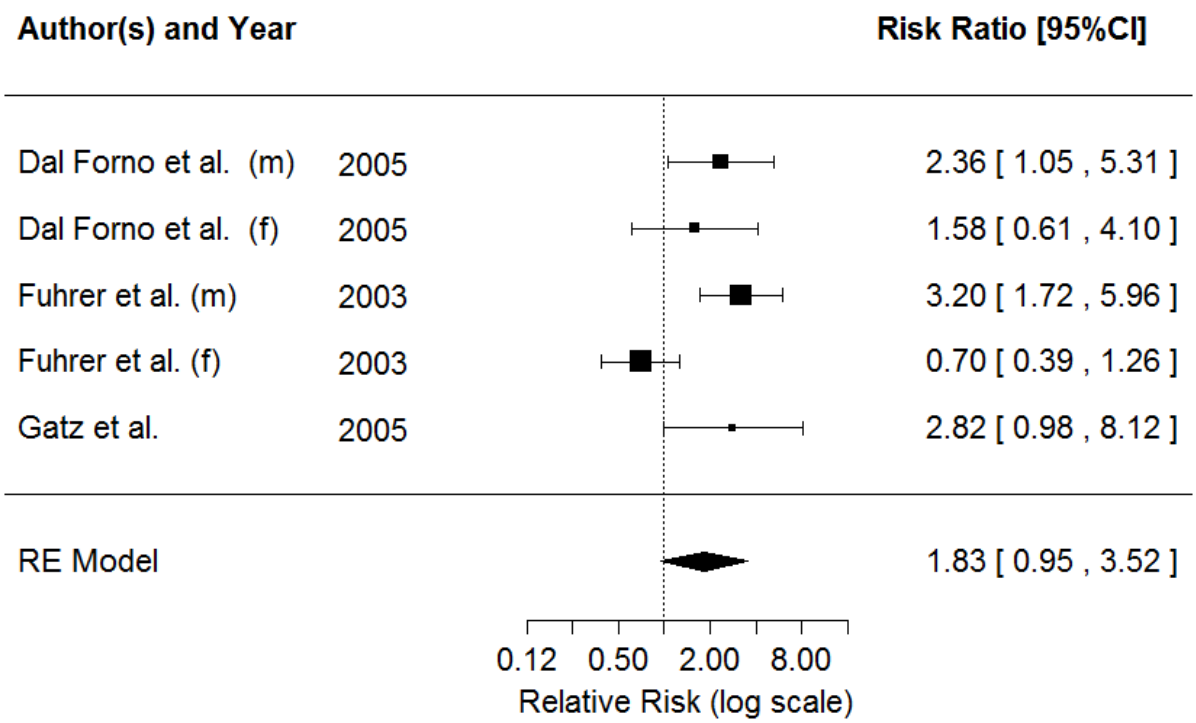
Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.5206	0.1344	3.8736	0.0001	0.2572	0.7840	***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1



Dementia categorical (CES-D >20)



Random-Effects Model (k = 5; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
-4.6477	9.2448	13.2954	12.5143	19.2954

tau^2 (estimated amount of total heterogeneity): 0.3891 (SE = 0.3983)
tau (square root of estimated tau^2 value): 0.6238
I^2 (total heterogeneity / total variability): 71.85%
H^2 (total variability / sampling variability): 3.55

Test for Heterogeneity:
Q(df = 4) = 14.2079, p-val = 0.0067

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.6033	0.3337	1.8080	0.0706	-0.0507	1.2574	.

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.5467	0.4162	1.3135	0.189	-0.2691	1.3625	13.4257	0.0038	0.5237	77.6548	4.4752
2	0.6427	0.4113	1.5627	0.1181	-0.1634	1.4487	14.1859	0.0027	0.5217	78.8523	4.7286
3	0.4305	0.3577	1.2035	0.2288	-0.2706	1.1316	8.5327	0.0362	0.3257	64.8412	2.8442

4	0.9413	0.2066	4.5557	0	0.5363	1.3462	1.5507	0.6706	0	0	1
5	0.5201	0.3882	1.3399	0.1803	-0.2407	1.2808	13.2095	0.0042	0.4585	77.289	4.4032

Fail-safe N Calculation Using the Rosenthal Approach

Observed Significance Level: 0.0005
Target Significance Level: 0.05
Fail-safe N: 16

Trim-and-fill analysis

Estimated number of missing studies on the left side: 1 (SE = 1.7009)

Random-Effects Model (k = 6; tau^2 estimator: DL)

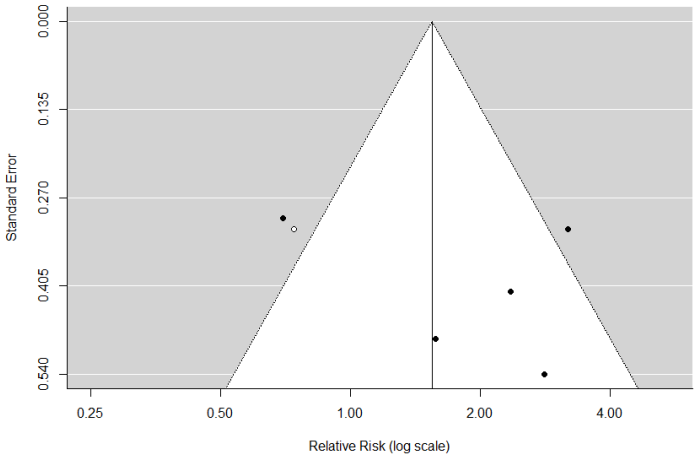
tau^2 (estimated amount of total heterogeneity): 0.4046 (SE = 0.3582)
tau (square root of estimated tau^2 value): 0.6361
I^2 (total heterogeneity / total variability): 74.33%
H^2 (total variability / sampling variability): 3.90

Test for Heterogeneity:
Q(df = 5) = 19.4798, p-val = 0.0016

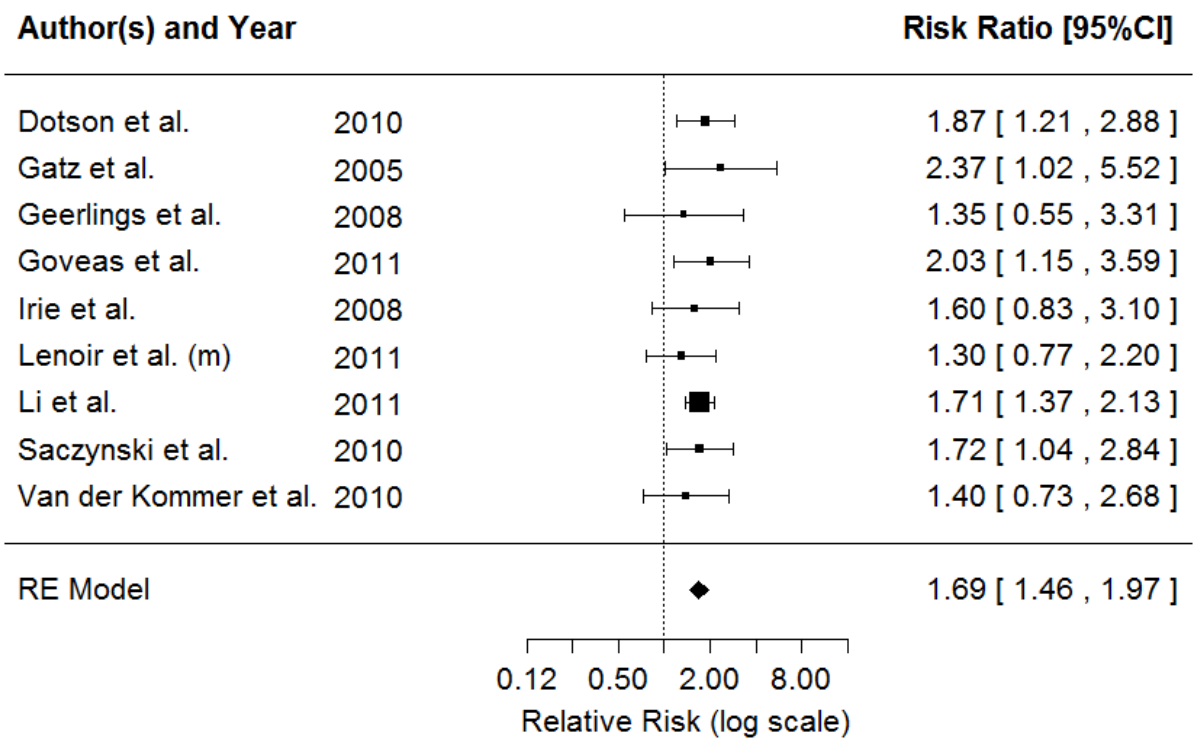
Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
0.4367	0.3056	1.4292	0.1529	-0.1622	1.0356

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1



Dementia categorical (CES-D >16)



Random-Effects Model (k = 9; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
1.7584	2.7745	0.4832	0.8776	2.4832

tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.0322)
tau (square root of estimated tau^2 value): 0
I^2 (total heterogeneity / total variability): 0.00%
H^2 (total variability / sampling variability): 1.00

Test for Heterogeneity:
Q(df = 8) = 2.7745, p-val = 0.9477

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.5268	0.0771	6.8328	<.0001	0.3757	0.6779	***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.5131	0.0823	6.2378	0	0.3519	0.6743	2.5459	0.9236	0	0	1
2	0.5157	0.0784	6.5817	0	0.3622	0.6693	2.1484	0.9512	0	0	1
3	0.5335	0.0782	6.8198	0	0.3801	0.6868	2.5213	0.9255	0	0	1
4	0.5131	0.08	6.4179	0	0.3564	0.6698	2.3577	0.9374	0	0	1
5	0.5299	0.0792	6.6914	0	0.3747	0.6852	2.7445	0.9076	0	0	1
6	0.5504	0.0805	6.8402	0	0.3927	0.7081	1.725	0.9735	0	0	1

7	0.5183	0.1058	4.8982	0	0.3109	0.7256	2.7606	0.9062	0	0	1
8	0.5253	0.0808	6.4972	0	0.3668	0.6837	2.7705	0.9054	0	0	1
9	0.5377	0.0793	6.7826	0	0.3824	0.6931	2.4244	0.9327	0	0	1

Fail-safe N Calculation Using the Rosenthal Approach

Observed Significance Level: <.0001
Target Significance Level: 0.05
Fail-safe N: 114

Trim-and-fill analysis

Estimated number of missing studies on the right side: 0 (SE = 2.0456)

Random-Effects Model (k = 9; tau^2 estimator: DL)

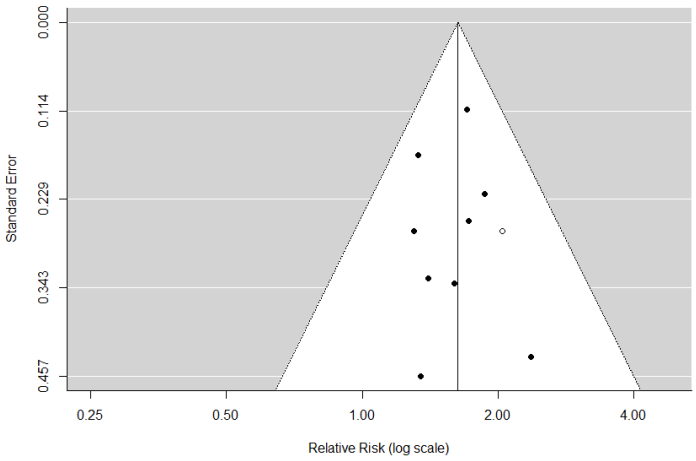
tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.0322)
tau (square root of estimated tau^2 value): 0
I^2 (total heterogeneity / total variability): 0.00%
H^2 (total variability / sampling variability): 1.00

Test for Heterogeneity:
Q(df = 8) = 2.7745, p-val = 0.9477

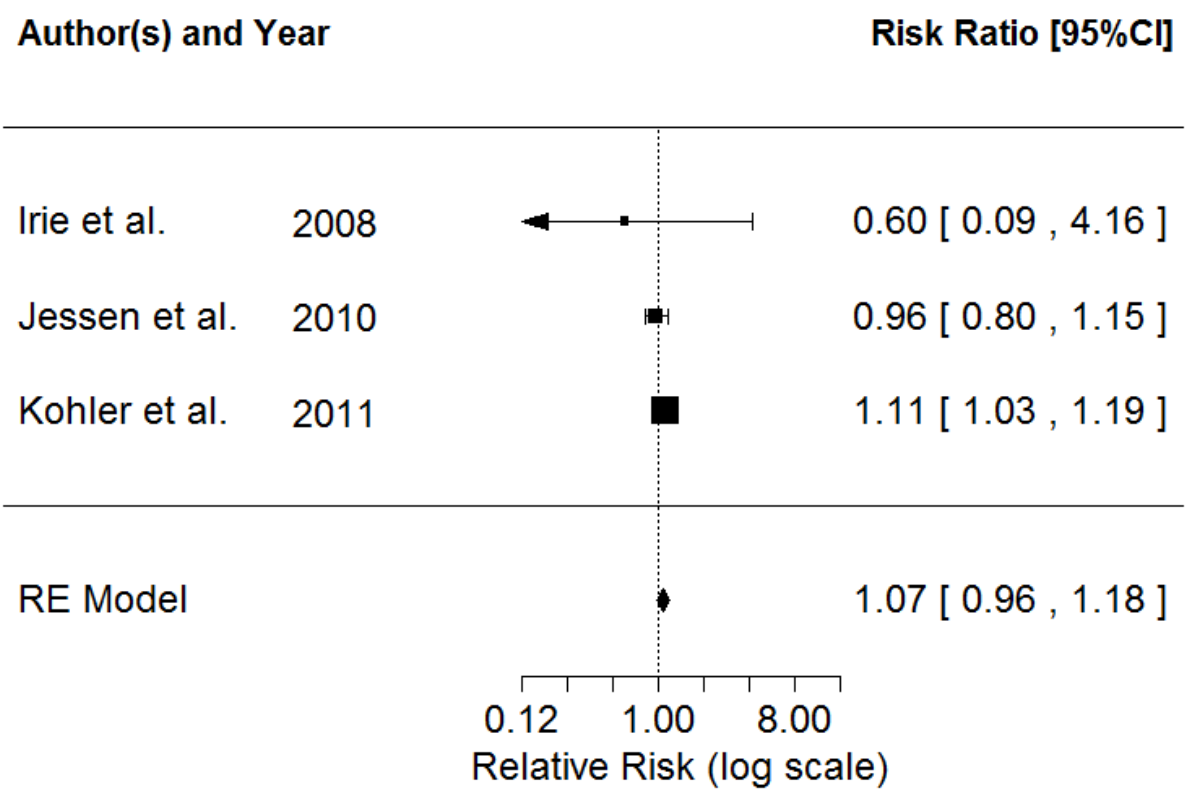
Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.5268	0.0771	6.8328	<.0001	0.3757	0.6779	***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1



VaD continuous (All)



Random-Effects Model (k = 3; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
1.3925	3.1371	1.2149	-0.5879	13.2149

tau^2 (estimated amount of total heterogeneity): 0.0027 (SE = 0.0124)
tau (square root of estimated tau^2 value): 0.0521
I^2 (total heterogeneity / total variability): 22.36%
H^2 (total variability / sampling variability): 1.29

Test for Heterogeneity:
Q(df = 2) = 2.5760, p-val = 0.2758

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
0.0631	0.0544	1.1599	0.2461	-0.0435	0.1696

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.5017	0.4457	1.1258	0.2602	-0.3717	1.3752	12.9869	0.0015	0.5039	84.5999	6.4934
2	0.4038	0.4305	0.938	0.3482	-0.44	1.2476	8.5973	0.0136	0.415	76.737	4.2987
3	0.9324	0.1994	4.6768	0	0.5417	1.3232	1.1598	0.56	0	0	1

4	0.5834	0.5536	1.0538	0.292	-0.5017	1.6685	13.4257	0.0012	0.7673	85.1032	6.7129

Fail-safe N Calculation Using the Rosenthal Approach

Fail-safe N Calculation Using the Rosenthal Approach
Observed Significance Level: 0.0003
Target Significance Level: 0.05
Fail-safe N: 14

Trim-and-fill analysis

Estimated number of missing studies on the left side: 1 (SE = 1.6103)

Random-Effects Model (k = 5; tau^2 estimator: DL)

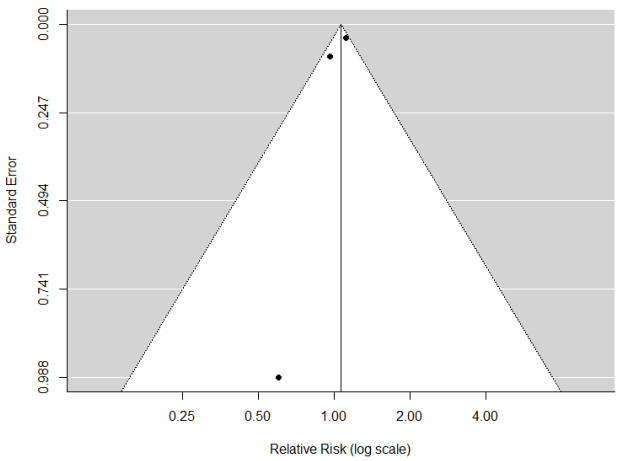
tau^2 (estimated amount of total heterogeneity): 0.4494 (SE = 0.4100)
tau (square root of estimated tau^2 value): 0.6704
I^2 (total heterogeneity / total variability): 80.15%
H^2 (total variability / sampling variability): 5.04

Test for Heterogeneity:
Q(df = 4) = 20.1561, p-val = 0.0005

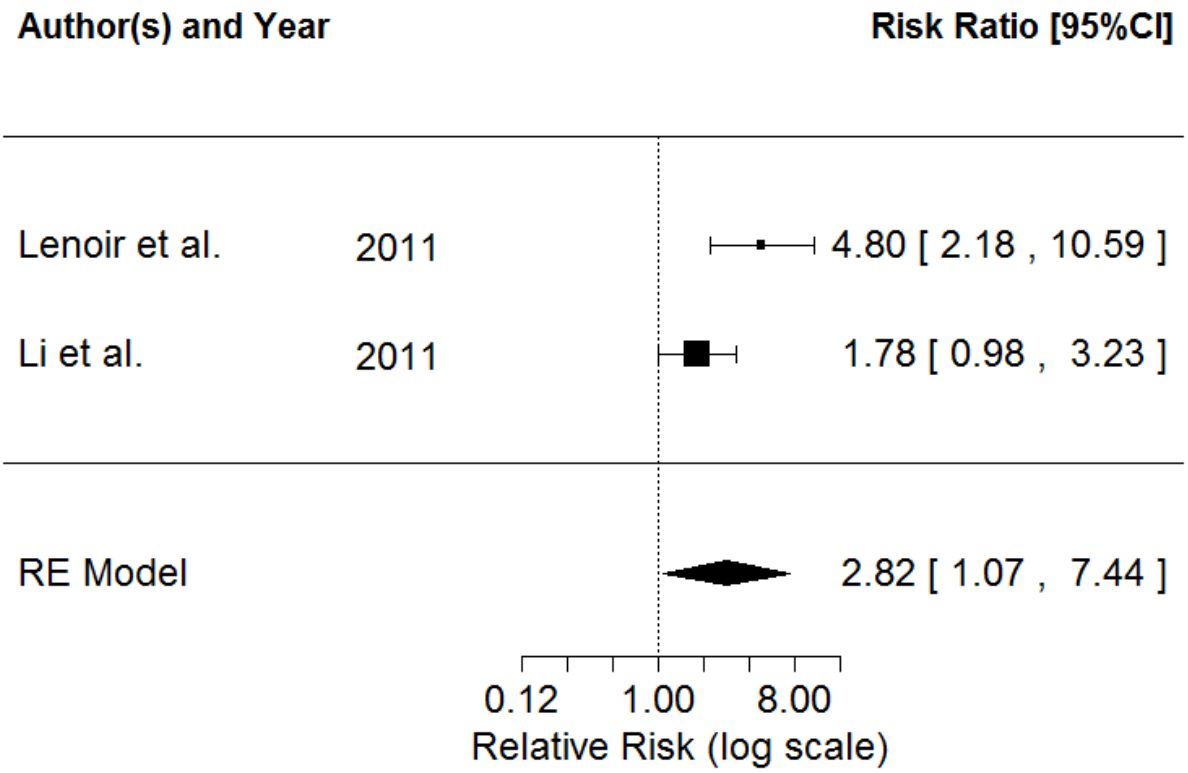
Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
0.4056	0.3388	1.1969	0.2313	-0.2585	1.0697

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1



VaD categorical (All)



Random-Effects Model (k = 2; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
-1.6261	3.7765	7.2522	4.6385	19.2522

tau^2 (estimated amount of total heterogeneity): 0.3646 (SE = 0.6958)
tau (square root of estimated tau^2 value): 0.6038
I^2 (total heterogeneity / total variability): 74.10%
H^2 (total variability / sampling variability): 3.86

Test for Heterogeneity:
Q(df = 1) = 3.8603, p-val = 0.0494

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
1.0370	0.4947	2.0961	0.0361	0.0673	2.0066	*

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Fail-safe N Calculation Using the Rosenthal Approach

Fail-safe N Calculation Using the Rosenthal Approach
Observed Significance Level: <.0001
Target Significance Level: 0.05
Fail-safe N: 11

Table ST1. Search strategy

PubMed	
1	(((Depress* OR Clinical depression OR Mood disorder OR Major depressive episode OR Dysthymi* OR Affective disorder OR Anxiety OR Generalised Anxiety Disorder OR GAD OR Phobia OR Panic disorder OR Panic attack OR Agoraphobia OR Social anxiety disorder OR Obsessive compulsive disorder OR Obsessive-compulsive disorder OR OCD OR PTSD OR Post traumatic stress disorder OR Post-traumatic stress disorder OR Alprazolam OR Benzodiazepines OR Anthramycin OR Bromazepam OR Clonazepam OR Devazepide OR Diazepam OR Flumazenil OR Flunitrazepam OR Flurazepam OR Lorazepam OR Nitrazepam OR Oxazepam OR Pirenzepine OR Prazepam OR Temazepam OR Chlordiazepoxide OR Clorazepate OR Dipotassium OR Estazolam OR Medazepam OR Midazolam OR Triazolam OR Psychotropic Drugs OR Antidepressive Agents OR Antidepressive Agents (Second-Generation) OR Antidepressive Agents (Tricyclic) OR Hallucinogens OR Tranquilizing Agents OR Anti-Anxiety Agents OR Antimanic Agents OR Antipsychotic Agents))) AND ((Cognit* OR Memory OR Attention OR Reaction time OR Speed of processing OR processing speed OR Crystallized ability OR Crystallized intelligence OR Fluid ability OR Fluid intelligence OR General mental ability OR GMA OR Intelligence OR Executive function OR Neuropsychological testing OR Mini mental stat* exam* OR MMSE OR Dementia OR Alzheimer* OR Mild cognitive impairment OR MCI)) AND (Humans[Mesh])
Ovid PsycINFO	
1	(Depress* or Clinical depression or Mood disorder or Major depressive episode or Dysthymi* or Affective disorder or Anxiety or Generalised Anxiety Disorder or GAD or Phobia or Panic disorder or Panic attack or Agoraphobia or Social anxiety disorder or Obsessive compulsive disorder or OCD or PTSD or Post traumatic stress disorder or Alprazolam or Benzodiazepines or Anthramycin or Bromazepam or Clonazepam or Devazepide or Diazepam or Flumazenil or Flunitrazepam or Flurazepam or Lorazepam or Nitrazepam or Oxazepam or Pirenzepine or Prazepam or Temazepam or Chlordiazepoxide or Clorazepate or Dipotassium or Estazolam or Medazepam or Midazolam or Triazolam or Psychotropic Drugs or Antidepressive Agents or Antidepressive Agents Second generation or Antidepressive Agents Tricyclic or Hallucinogens or Tranquilizing Agents or Anti Anxiety Agents or Antimanic Agents or Antipsychotic Agents).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
2	(Cognit* or Memory or Attention or Reaction time or Speed of processing or processing speed or Crystallized ability or Crystallized intelligence or Fluid ability or Fluid intelligence or General mental ability or GMA or Intelligence or Executive function or Neuropsychological testing or Mini mental stat* exam* or MMSE or Dementia or Alzheimer* or Mild cognitive impairment or MCI).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
3	1 and 2
4	limit 3 to (human and English language)
Cochrane library	
1	'Depress* OR Clinical depression OR Mood disorder OR Major depressive episode OR Dysthymi* OR Affective disorder OR Anxiety OR Generalised Anxiety Disorder OR GAD OR Phobia OR Panic disorder OR Panic attack OR Agoraphobia OR Social anxiety disorder OR Obsessive compulsive disorder OR Obsessive-compulsive disorder OR OCD OR PTSD OR Post traumatic stress disorder OR Post-traumatic stress disorder OR Alprazolam OR Benzodiazepines OR Anthramycin OR Bromazepam OR Clonazepam OR Devazepide OR Diazepam OR Flumazenil OR Flunitrazepam OR Flurazepam OR Lorazepam OR Nitrazepam OR

	Oxazepam OR Pirenzepine OR Prazepam OR Temazepam OR Chlordiazepoxide OR Clorazepate OR Dipotassium OR Estazolam OR Medazepam OR Midazolam OR Triazolam OR Psychotropic Drugs OR Antidepressive Agents OR Antidepressive Agents (Second generation) OR Antidepressive Agents (Tricyclic) OR Hallucinogens OR Tranquilizing Agents OR Anti-Anxiety Agents OR Antimanic Agents OR Antipsychotic Agents and Cognit* OR Memory OR Attention OR Reaction time OR Speed of processing OR processing speed OR Crystallized ability OR Crystallized intelligence OR Fluid ability OR Fluid intelligence OR General mental ability OR GMA OR Intelligence OR Executive function OR Neuropsychological testing OR Mini mental stat* exam* OR MMSE OR Dementia OR Alzheimer* OR Mild cognitive impairment OR MCI

Table ST2. Quality rating of studies selected for inclusion based on the Newcastle-Ottawa Scale.

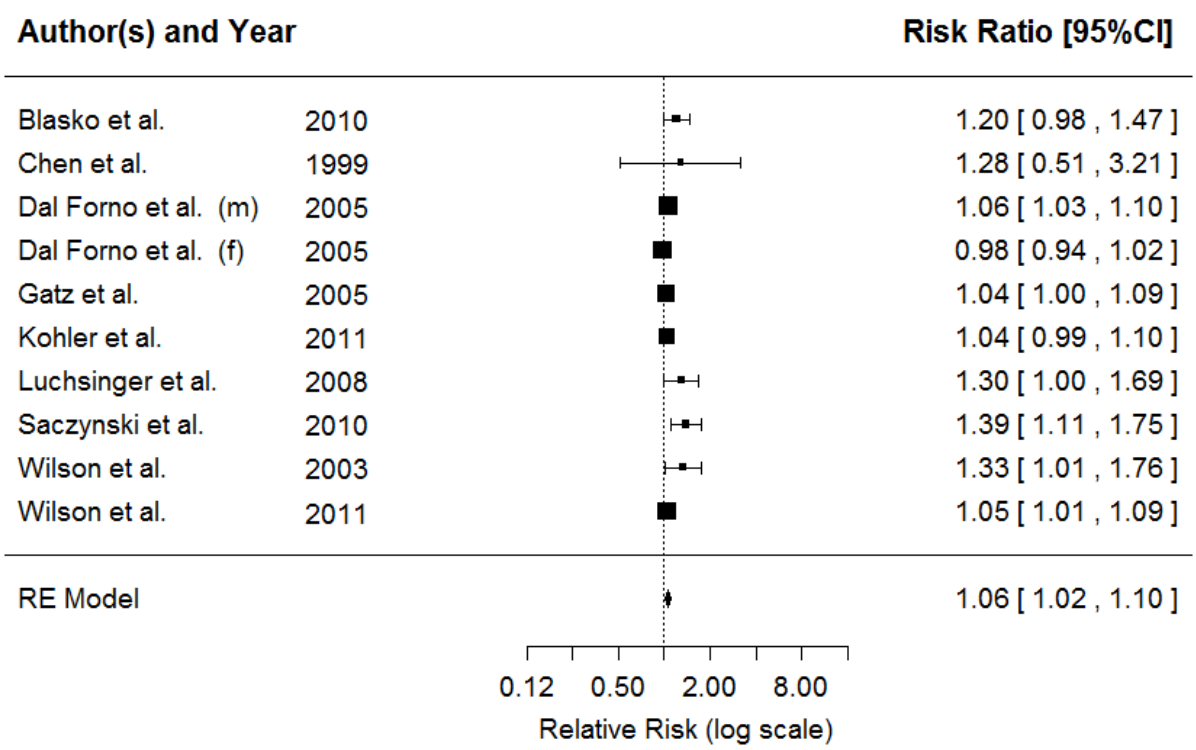
		Quality Indicators From the Newcastle-Ottawa Scale								
Studies		1	2	3	4	5	6	7	8	9
Barnes et al., 2012		Yes	yes	yes	yes	no	yes	yes	yes	yes
Becker et al., 2009		yes	yes	yes	yes	yes	yes	yes	yes	yes
Blasko et al., 2010		yes	yes	yes	yes	no	yes	yes	yes	yes
Chen et al., 1999		yes	yes	yes	yes	yes	yes	yes	yes	yes
Chen et al., 2008 (China)		no	yes	yes	yes	yes	yes	yes	yes	yes
Chen et al., 2008 (UK)		yes	yes	yes	yes	yes	yes	yes	yes	yes
Dal Forno et al., 2005		yes	yes	yes	yes	no	yes	yes	yes	no
Devanand et al., 1996		no	yes	yes	yes	yes	yes	yes	yes	yes
Dotson et al., 2010		yes	yes	yes	yes	yes	yes	yes	yes	no
Fuhrer et al., 2003		yes	yes	yes	yes	yes	yes	yes	yes	yes
Gatz et al., 2005		yes	yes	yes	yes	yes	yes	yes	yes	yes
Geerlings et al., 2008		yes	yes	yes	yes	yes	yes	yes	yes	no
Geerlings et al., 2000		yes	yes	yes	yes	yes	yes	yes	yes	yes
Goveas et al., 2011		no	yes	yes	yes	no	yes	yes	yes	yes
Heser et al., 2013		yes	yes	yes	yes	yes	yes	yes	yes	yes
Heun et al.,		yes	yes	yes	yes	yes	yes	yes	yes	yes

2006										
Irie et al., 2008		no	yes	yes	yes	no	yes	yes	yes	yes
Jessen et al., 2010		yes	yes	yes	yes	yes	yes	yes	yes	yes
Jessen et al., 2011		yes	yes	yes	yes	yes	yes	yes	yes	yes
Jungwirth et al., 2009		yes	yes	yes	yes	no	no	yes	yes	yes
Kim et al., 2010		yes	yes	yes	yes	yes	yes	yes	yes	yes
Kim et al., 2011		yes	yes	yes	yes	yes	yes	yes	yes	yes
Kohler et al., 2011		yes	yes	yes	yes	yes	yes	yes	yes	yes
Lenoir et al., 2011		yes	yes	yes	yes	yes	yes	yes	yes	yes
Li et al., 2011		yes	yes	yes	yes	yes	yes	yes	yes	yes
Luchsinger et al., 2008		yes	yes	yes	yes	yes	yes	yes	yes	no
Luppa et al., 2013		yes	yes	yes	yes	yes	yes	yes	yes	yes
Palmer et al., 2007		yes	yes	yes	yes	yes	yes	yes	yes	yes
Palsson et al., 1999		yes	yes	yes	yes	no	no	yes	yes	yes
Saczynski et al., 2010		yes	yes	yes	yes	yes	yes	yes	yes	no
Samieri et al., 2008		yes	yes	yes	yes	no	yes	yes	yes	yes
Schmand et al., 1997		yes	yes	yes	yes	no	no	yes	yes	yes
St John et al., 2002		yes	yes	yes	yes	yes	yes	yes	yes	yes
Van der Kommer et al., 2010		yes	yes	yes	yes	no	no	yes	yes	yes

Vilalta-Franch et al., 2012		yes	yes	yes	yes	yes	yes	yes	yes	yes
Wilson et al., 2003		yes	yes	yes	yes	yes	yes	yes	yes	yes
Wilson et al., 2011		yes	yes	yes	yes	yes	yes	yes	yes	yes
1. Cohort truly representative of the population 2. Non-exposed participants from same community as exposed participants 3. Ascertainment of exposure 4. Dementia not present at baseline 5. Study controls for age and sex 6. Study controls for other factors 7. Quality of outcome assessment 8. Follow-up long enough for dementia to occur 9. Complete follow-up (all participants are accounted for)										

Analyses:

AD continuous (all compatible)



Random-Effects Model (k = 10; tau^2 estimator: DL)

```
 logLik  deviance      AIC      BIC     AICc
 8.1673   22.1823  -12.3346  -11.7294  -10.6203

tau^2 (estimated amount of total heterogeneity): 0.0015 (SE = 0.0014)
tau (square root of estimated tau^2 value):      0.0391
I^2 (total heterogeneity / total variability):   62.06%
H^2 (total variability / sampling variability):  2.64

Test for Heterogeneity:
Q(df = 9) = 23.7240, p-val = 0.0048

Model Results:

estimate      se    zval    pval    ci.lb   ci.ub
  0.0536  0.0190  2.8217  0.0048   0.0164  0.0908      **

---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.0492	0.0189	2.5979	0.0094	0.0121	0.0863	21.8313	0.0052	0.0015	63.3553	2.7289
2	0.054	0.0194	2.7833	0.0054	0.016	0.0919	23.53	0.0027	0.0016	66.0008	2.9412

3	0.0586	0.024	2.437	0.0148	0.0115	0.1057	22.1508	0.0046	0.0022	63.8839	2.7688
4	0.0623	0.0165	3.7839	0.0002	0.0301	0.0946	13.2307	0.1042	0.0007	39.5346	1.6538
5	0.0619	0.0235	2.6365	0.0084	0.0159	0.108	23.7195	0.0026	0.0021	66.2725	2.9649
6	0.0601	0.0226	2.6605	0.0078	0.0158	0.1044	23.7212	0.0026	0.0019	66.2749	2.9651
7	0.0486	0.0184	2.6442	0.0082	0.0126	0.0847	21.0271	0.0071	0.0014	61.9539	2.6284
8	0.0438	0.0166	2.6455	0.0082	0.0114	0.0763	17.505	0.0253	0.001	54.2989	2.1881
9	0.0484	0.0182	2.6532	0.008	0.0126	0.0841	20.7307	0.0079	0.0013	61.4098	2.5913
10	0.061	0.0241	2.5344	0.0113	0.0138	0.1081	23.4956	0.0028	0.0022	65.951	2.9369

Fail-safe N Calculation Using the Rosenthal Approach

Fail-safe N Calculation Using the Rosenthal Approach
Observed Significance Level: <.0001
Target Significance Level: 0.05
Fail-safe N: 101

Trim-and-fill analysis

Estimated number of missing studies on the left side: 5 (SE = 1.9266)

Random-Effects Model (k = 15; tau^2 estimator: DL)

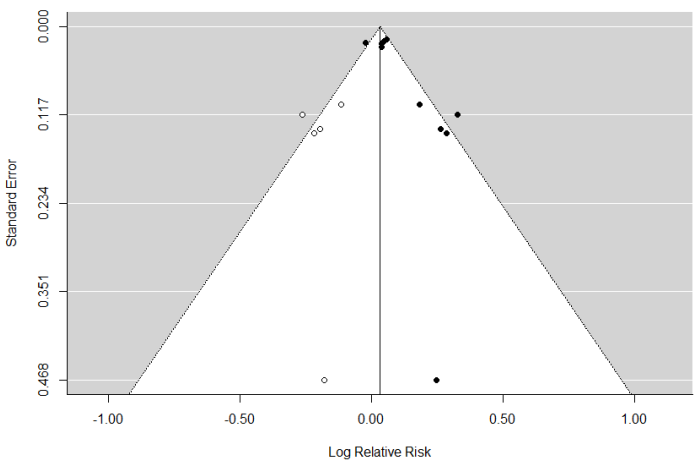
tau^2 (estimated amount of total heterogeneity): 0.0025 (SE = 0.0021)
tau (square root of estimated tau^2 value): 0.0501
I^2 (total heterogeneity / total variability): 64.10%
H^2 (total variability / sampling variability): 2.79

Test for Heterogeneity:
Q(df = 14) = 38.9936, p-val = 0.0004

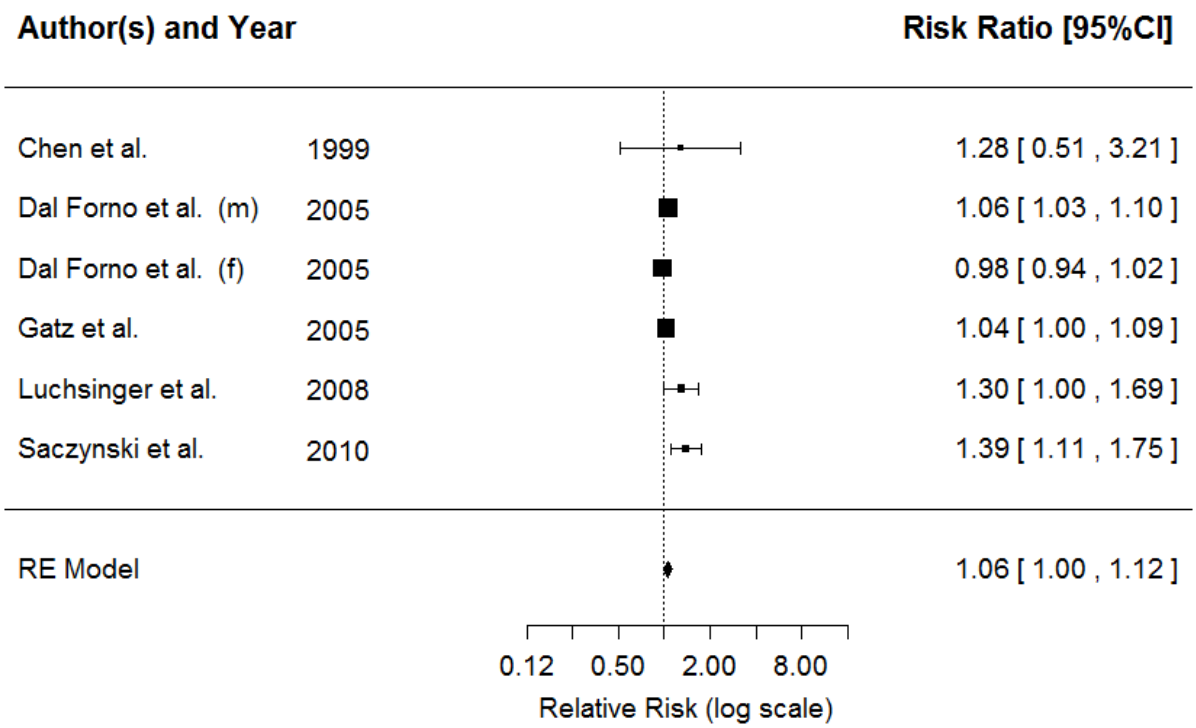
Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
0.0334	0.0215	1.5493	0.1213	-0.0088	0.0756

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1



AD continuous (CES-D/HAM)



Random-Effects Model (k = 7; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
3.5299	15.2687	-3.0598	-3.4762	0.9402

tau^2 (estimated amount of total heterogeneity): 0.0025 (SE = 0.0029)
tau (square root of estimated tau^2 value): 0.0505
I^2 (total heterogeneity / total variability): 72.87%
H^2 (total variability / sampling variability): 3.69

Test for Heterogeneity:
Q(df = 5) = 18.4272, p-val = 0.0025

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.0538	0.0297	1.8108	0.0702	-0.0044	0.1121	.

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.0661	0.0314	2.1066	0.0352	0.0046	0.1275	21.3265	0.0007	0.0031	76.555	4.2653
2	0.0928	0.0462	2.0118	0.0442	0.0024	0.1833	18.5071	0.0024	0.0056	72.9833	3.7014
3	0.0911	0.0325	2.8064	0.005	0.0275	0.1548	11.1795	0.0479	0.0022	55.2754	2.2359
4	0.0977	0.0453	2.1576	0.031	0.009	0.1865	21.5077	0.0006	0.0054	76.7525	4.3015

5	0.0544	0.03	1.8121	0.07	-0.0044	0.1133	18.7243	0.0022	0.0026	73.2967	3.7449
6	0.044	0.0269	1.6383	0.1014	-0.0086	0.0966	15.1112	0.0099	0.0019	66.9119	3.0222
7	0.0538	0.0297	1.8108	0.0702	-0.0044	0.1121	18.4272	0.0025	0.0025	72.8661	3.6854

Fail-safe N Calculation Using the Rosenthal Approach

Observed Significance Level: <.0001
Target Significance Level: 0.05
Fail-safe N: 43

Trim-and-fill analysis

Estimated number of missing studies on the left side: 3 (SE = 1.6850)

Random-Effects Model (k = 10; tau^2 estimator: DL)

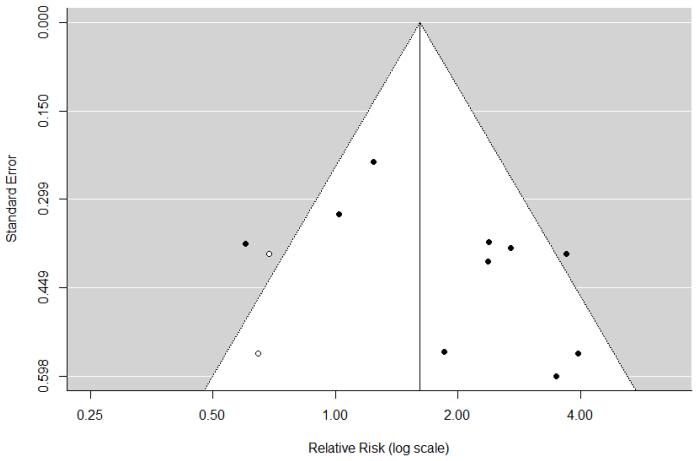
tau^2 (estimated amount of total heterogeneity): 0.0047 (SE = 0.0048)
tau (square root of estimated tau^2 value): 0.0686
I^2 (total heterogeneity / total variability): 74.45%
H^2 (total variability / sampling variability): 3.91

Test for Heterogeneity:
Q(df = 9) = 35.2272, p-val < .0001

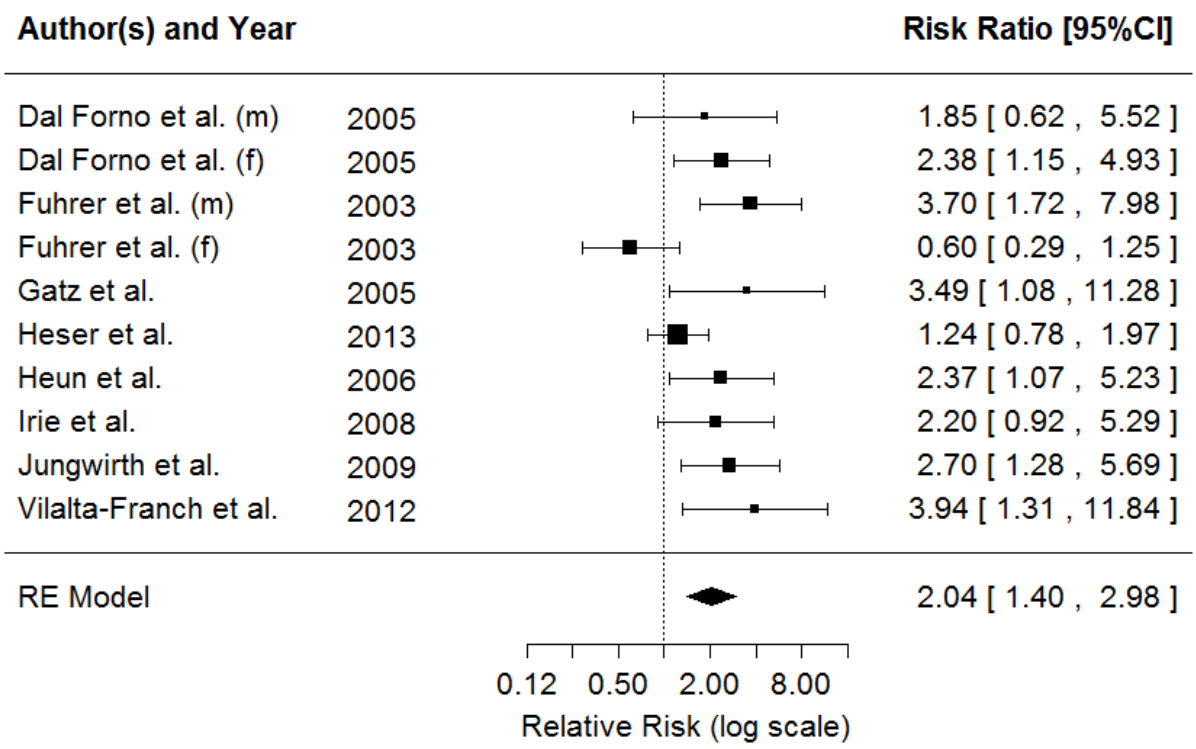
Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
0.0276	0.0339	0.8125	0.4165	-0.0389	0.0940

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1



AD Clinical Threshold (All compatible)



Random-Effects Model (k = 10; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
-8.5049	16.0360	21.0097	21.6149	22.7240

tau^2 (estimated amount of total heterogeneity): 0.1929 (SE = 0.1725)
tau (square root of estimated tau^2 value): 0.4392
I^2 (total heterogeneity / total variability): 54.92%
H^2 (total variability / sampling variability): 2.22

Test for Heterogeneity:
Q(df = 9) = 19.9626, p-val = 0.0181

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.7138	0.1924	3.7096	0.0002	0.3367	1.0910	***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.0492	0.0189	2.5979	0.0094	0.0121	0.0863	21.8313	0.0052	0.0015	63.3553	2.7289
2	0.054	0.0194	2.7833	0.0054	0.016	0.0919	23.53	0.0027	0.0016	66.0008	2.9412
3	0.0586	0.024	2.437	0.0148	0.0115	0.1057	22.1508	0.0046	0.0022	63.8839	2.7688
4	0.0623	0.0165	3.7839	0.0002	0.0301	0.0946	13.2307	0.1042	0.0007	39.5346	1.6538
5	0.0619	0.0235	2.6365	0.0084	0.0159	0.108	23.7195	0.0026	0.0021	66.2725	2.9649
6	0.0601	0.0226	2.6605	0.0078	0.0158	0.1044	23.7212	0.0026	0.0019	66.2749	2.9651

7	0.0486	0.0184	2.6442	0.0082	0.0126	0.0847	21.0271	0.0071	0.0014	61.9539	2.6284
8	0.0438	0.0166	2.6455	0.0082	0.0114	0.0763	17.505	0.0253	0.001	54.2989	2.1881
9	0.0484	0.0182	2.6532	0.008	0.0126	0.0841	20.7307	0.0079	0.0013	61.4098	2.5913
10	0.061	0.0241	2.5344	0.0113	0.0138	0.1081	23.4956	0.0028	0.0022	65.951	2.9369

Fail-safe N Calculation Using the Rosenthal Approach

Observed Significance Level: <.0001
Target Significance Level: 0.05
Fail-safe N: 102

Trim-and-fill analysis

Estimated number of missing studies on the left side: 3 (SE = 2.1498)

Random-Effects Model (k = 13; tau^2 estimator: DL)

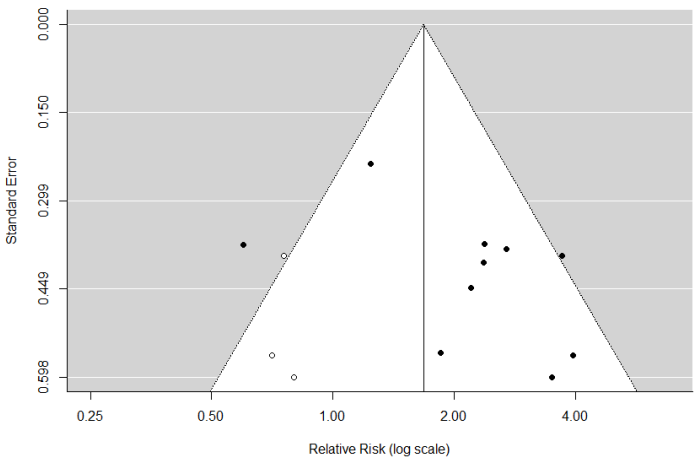
tau^2 (estimated amount of total heterogeneity): 0.2369 (SE = 0.1753)
tau (square root of estimated tau^2 value): 0.4867
I^2 (total heterogeneity / total variability): 58.01%
H^2 (total variability / sampling variability): 2.38

Test for Heterogeneity:
Q(df = 12) = 28.5795, p-val = 0.0045

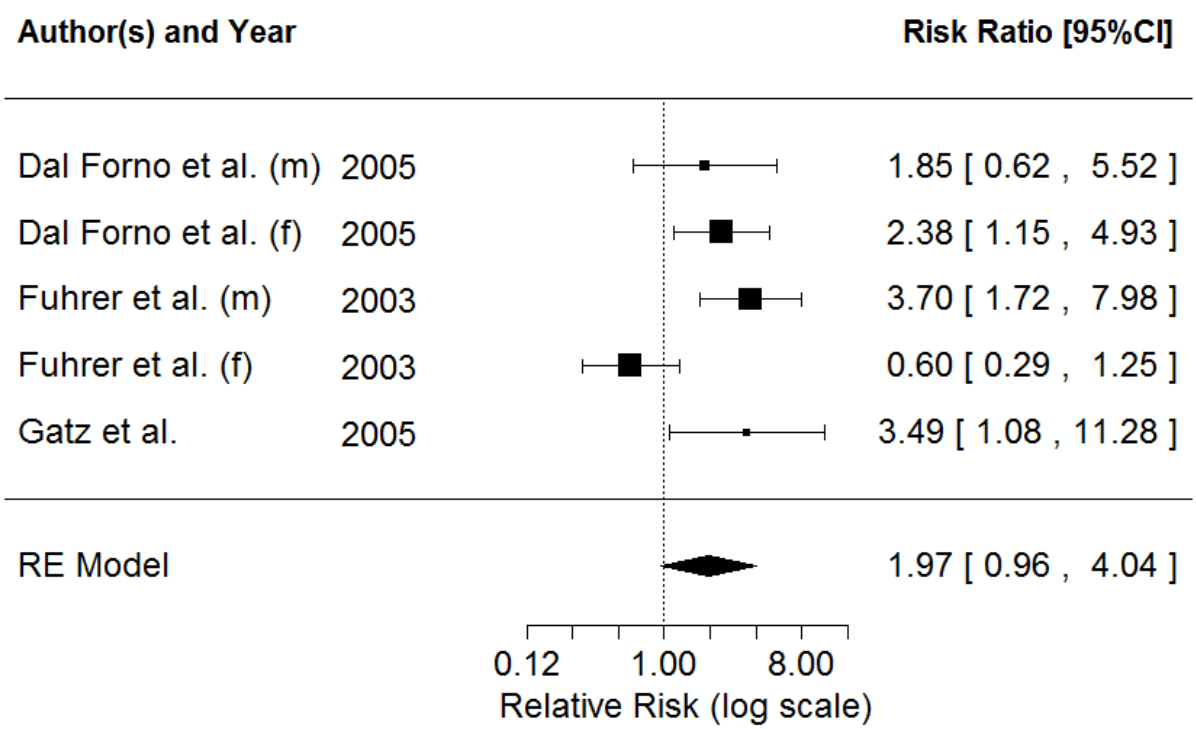
Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.5181	0.1823	2.8415	0.0045	0.1607	0.8755	**

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’



AD Clinical Threshold (CES-D > 20)



Random-Effects Model (k = 5; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
-5.3513	9.5265	14.7026	13.9215	20.7026

tau^2 (estimated amount of total heterogeneity): 0.4698 (SE = 0.4821)
tau (square root of estimated tau^2 value): 0.6854
I^2 (total heterogeneity / total variability): 70.96%
H^2 (total variability / sampling variability): 3.44

Test for Heterogeneity:
Q(df = 4) = 13.7733, p-val = 0.0081

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.6757	0.3682	1.8351	0.0665	-0.0460	1.3973	.

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.6953	0.4513	1.5407	0.1234	-0.1892	1.5798	13.7733	0.0032	0.6264	78.2188	4.5911
2	0.6327	0.4892	1.2933	0.1959	-0.3262	1.5915	13.1567	0.0043	0.726	77.1979	4.3856
3	0.4993	0.414	1.2061	0.2278	-0.3121	1.3107	9.6725	0.0216	0.4626	68.9843	3.2242
4	1.0257	0.225	4.5583	0	0.5847	1.4667	1.3841	0.7093	0	0	1
5	0.5639	0.4242	1.3295	0.1837	-0.2674	1.3952	12.527	0.0058	0.5404	76.0517	4.1757

Fail-safe N Calculation Using the Rosenthal Approach

Observed Significance Level: 0.0004
Target Significance Level: 0.05

Fail-safe N: 16

Trim-and-fill analysis

Estimated number of missing studies on the left side: 1 (SE = 1.7009)

Random-Effects Model (k = 6; tau^2 estimator: DL)

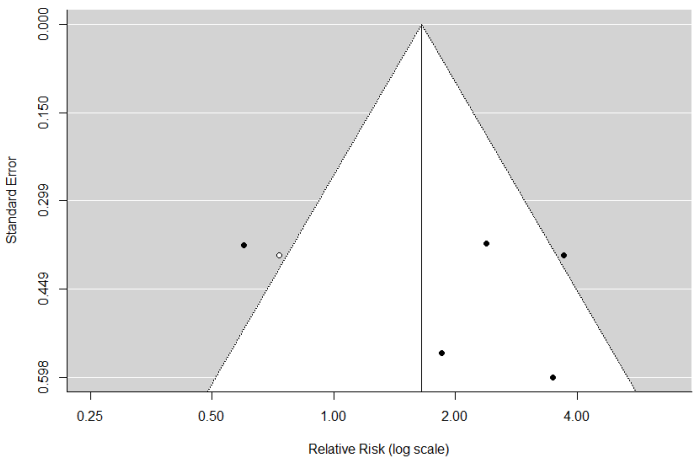
tau^2 (estimated amount of total heterogeneity): 0.4876 (SE = 0.4359)
tau (square root of estimated tau^2 value): 0.6983
I^2 (total heterogeneity / total variability): 72.65%
H^2 (total variability / sampling variability): 3.66

Test for Heterogeneity:
Q(df = 5) = 18.2798, p-val = 0.0026

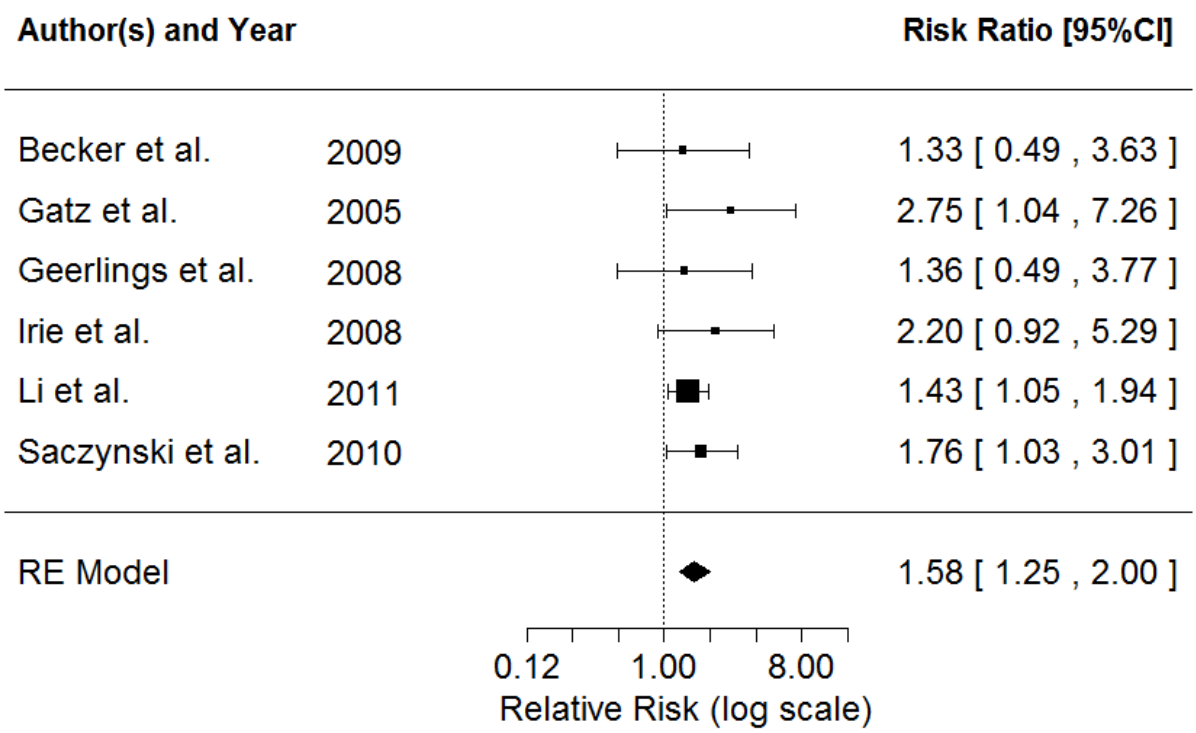
Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
0.5005	0.3382	1.4801	0.1389	-0.1623	1.1633

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1



AD Clinical Threshold (CES-D > 16)



Random-Effects Model (k = 6; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
-0.8119	2.5581	5.6239	5.2074	9.6239

tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.0724)
tau (square root of estimated tau^2 value): 0
I^2 (total heterogeneity / total variability): 0.00%
H^2 (total variability / sampling variability): 1.00

Test for Heterogeneity:
Q(df = 5) = 2.5581, p-val = 0.7677

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.4585	0.1189	3.8561	0.0001	0.2255	0.6916	***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.5958	0.1827	3.2608	0.0011	0.2377	0.954	1.5787	0.8126	0	0	1
2	0.4684	0.1222	3.8315	0.0001	0.2288	0.708	2.4371	0.6559	0	0	1
3	0.4247	0.1225	3.4667	0.0005	0.1846	0.6648	1.2333	0.8726	0	0	1
4	0.4669	0.1221	3.8221	0.0001	0.2275	0.7063	2.469	0.6502	0	0	1
5	0.4335	0.1233	3.5142	0.0004	0.1917	0.6752	1.9731	0.7407	0	0	1
6	0.4337	0.132	3.2844	0.001	0.1749	0.6924	2.3703	0.668	0	0	1

Fail-safe N Calculation Using the Rosenthal Approach

Fail-safe N Calculation Using the Rosenthal Approach
Observed Significance Level: <.0001
Target Significance Level: 0.05
Fail-safe N: 26

Estimated number of missing studies on the left side: 0 (SE = 1.6829)

Estimated number of missing studies on the left side: 2 (SE = 1.7837)

Random-Effects Model (k = 8; tau^2 estimator: DL)

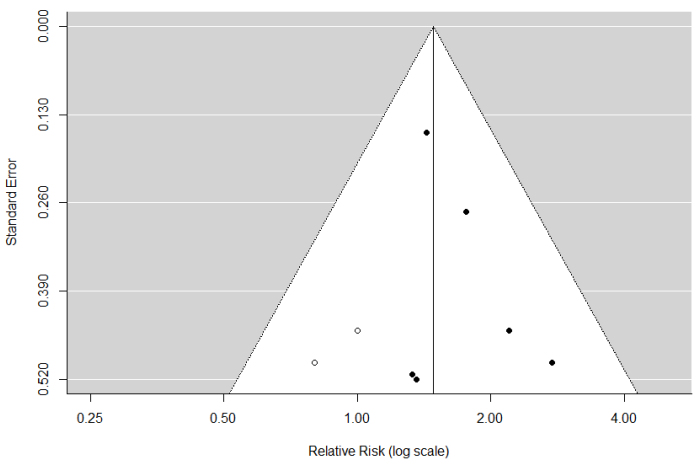
tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.0676)
tau (square root of estimated tau^2 value): 0
I^2 (total heterogeneity / total variability): 0.00%
H^2 (total variability / sampling variability): 1.00

Test for Heterogeneity:
Q(df = 7) = 5.1651, p-val = 0.6398

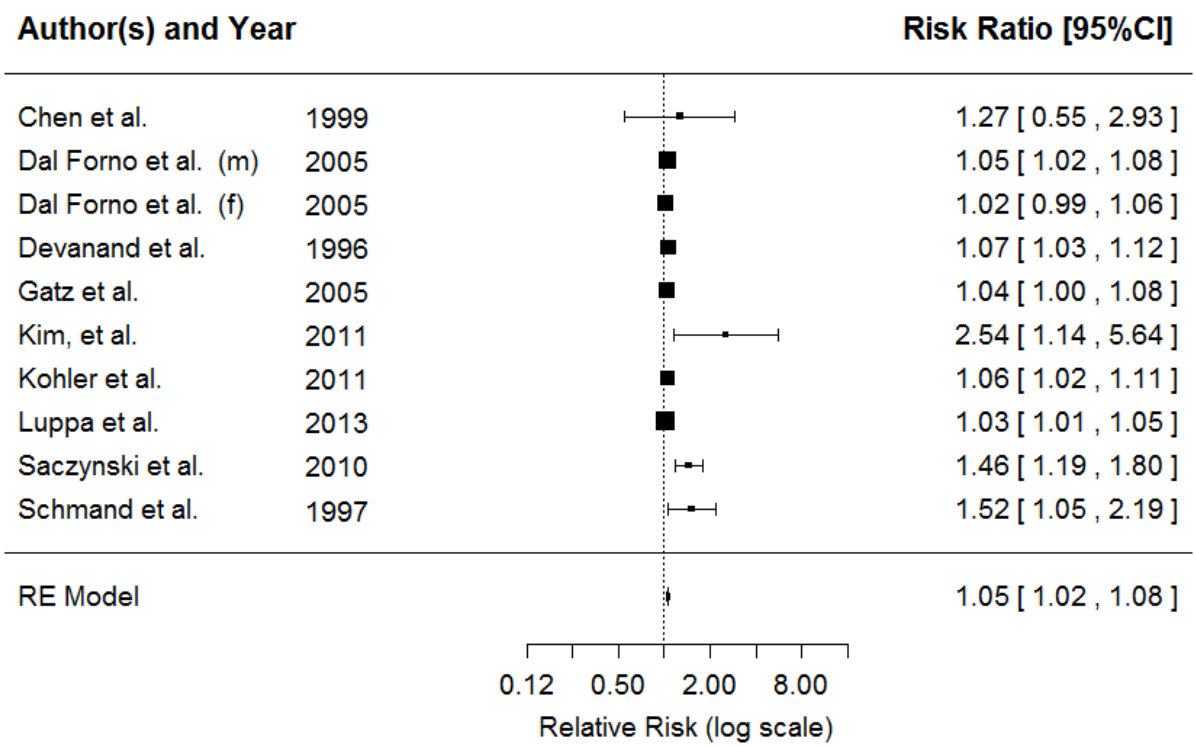
Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.3952	0.1119	3.5302	0.0004	0.1758	0.6146	***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1



Dementia continuous (all compatible)



Random-Effects Model (k = 10; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
7.1882	27.5279	-10.3764	-9.7712	-8.6621

tau^2 (estimated amount of total heterogeneity): 0.0008 (SE = 0.0007)
tau (square root of estimated tau^2 value): 0.0284
I^2 (total heterogeneity / total variability): 63.06%
H^2 (total variability / sampling variability): 2.71

Test for Heterogeneity:
Q(df = 9) = 24.3653, p-val = 0.0038

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.0508	0.0135	3.7672	0.0002	0.0244	0.0772	***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.0492	0.0189	2.5979	0.0094	0.0121	0.0863	21.8313	0.0052	0.0015	63.3553	2.7289
2	0.054	0.0194	2.7833	0.0054	0.016	0.0919	23.53	0.0027	0.0016	66.0008	2.9412
3	0.0586	0.024	2.437	0.0148	0.0115	0.1057	22.1508	0.0046	0.0022	63.8839	2.7688
4	0.0623	0.0165	3.7839	0.0002	0.0301	0.0946	13.2307	0.1042	0.0007	39.5346	1.6538
5	0.0619	0.0235	2.6365	0.0084	0.0159	0.108	23.7195	0.0026	0.0021	66.2725	2.9649
6	0.0601	0.0226	2.6605	0.0078	0.0158	0.1044	23.7212	0.0026	0.0019	66.2749	2.9651
7	0.0486	0.0184	2.6442	0.0082	0.0126	0.0847	21.0271	0.0071	0.0014	61.9539	2.6284

8	0.0438	0.0166	2.6455	0.0082	0.0114	0.0763	17.505	0.0253	0.001	54.2989	2.1881
9	0.0484	0.0182	2.6532	0.008	0.0126	0.0841	20.7307	0.0079	0.0013	61.4098	2.5913
10	0.061	0.0241	2.5344	0.0113	0.0138	0.1081	23.4956	0.0028	0.0022	65.951	2.9369

Fail-safe N Calculation Using the Rosenthal Approach

Observed Significance Level: <.0001
Target Significance Level: 0.05
Fail-safe N: 121

Trim-and-fill analysis

Estimated number of missing studies on the left side: 3 (SE = 2.3645)

Random-Effects Model (k = 15; tau^2 estimator: DL)

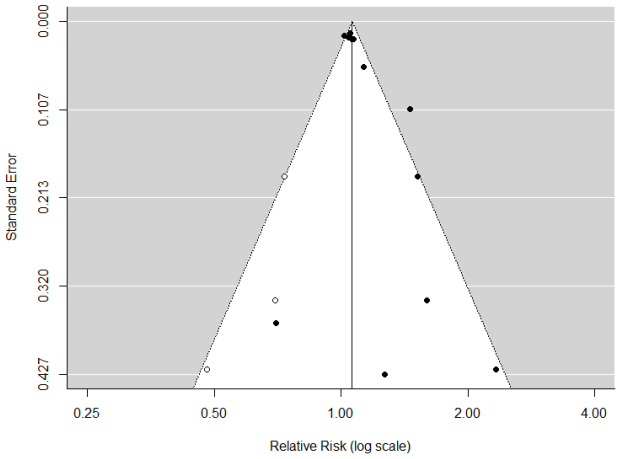
tau^2 (estimated amount of total heterogeneity): 0.0017 (SE = 0.0015)
tau (square root of estimated tau^2 value): 0.0409
I^2 (total heterogeneity / total variability): 59.23%
H^2 (total variability / sampling variability): 2.45

Test for Heterogeneity:
Q(df = 14) = 34.3394, p-val = 0.0018

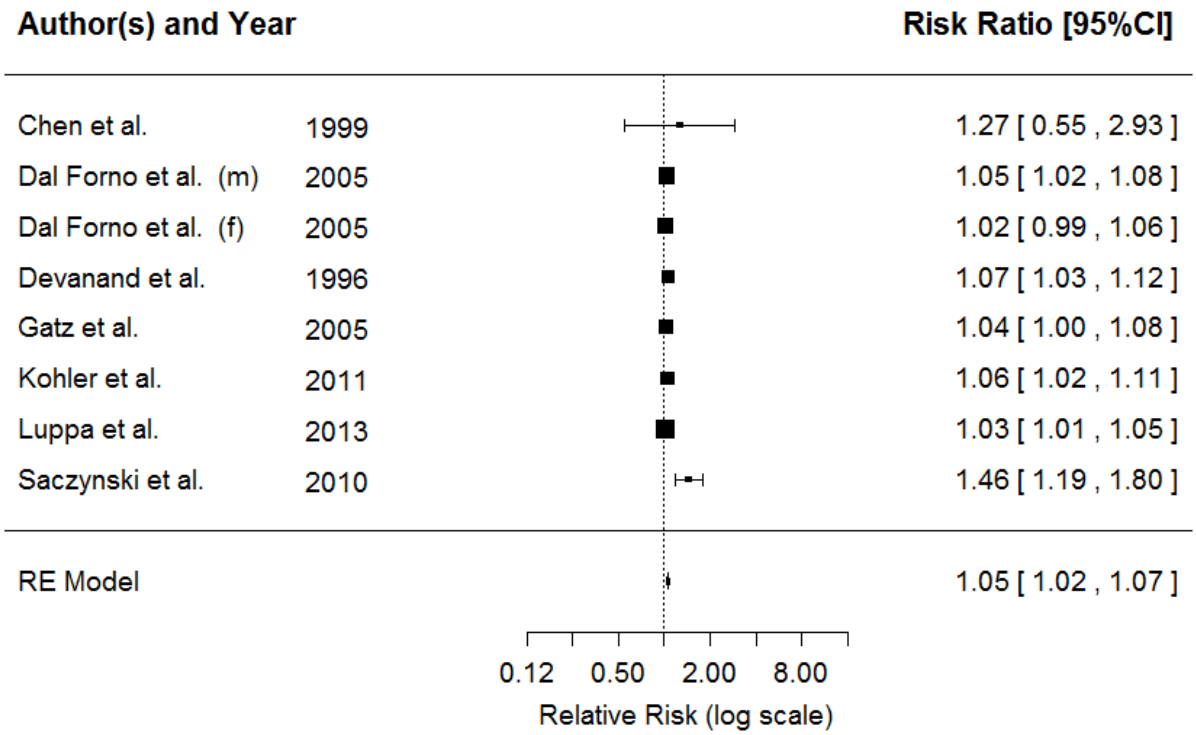
Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.0606	0.0188	3.2296	0.0012	0.0238	0.0974	**

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1



Dementia continuous (CES-D/HAM)



Random-Effects Model (k = 8; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
11.3939	17.6476	-18.7878	-18.6290	-16.3878

tau^2 (estimated amount of total heterogeneity): 0.0004 (SE = 0.0005)
tau (square root of estimated tau^2 value): 0.0211
I^2 (total heterogeneity / total variability): 54.82%
H^2 (total variability / sampling variability): 2.21

Test for Heterogeneity:
Q(df = 7) = 15.4937, p-val = 0.0302

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.0457	0.0111	4.1261	<.0001	0.0240	0.0674	***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.0492	0.0189	2.5979	0.0094	0.0121	0.0863	21.8313	0.0052	0.0015	63.3553	2.7289
2	0.054	0.0194	2.7833	0.0054	0.016	0.0919	23.53	0.0027	0.0016	66.0008	2.9412
3	0.0586	0.024	2.437	0.0148	0.0115	0.1057	22.1508	0.0046	0.0022	63.8839	2.7688
4	0.0623	0.0165	3.7839	0.0002	0.0301	0.0946	13.2307	0.1042	0.0007	39.5346	1.6538
5	0.0619	0.0235	2.6365	0.0084	0.0159	0.108	23.7195	0.0026	0.0021	66.2725	2.9649
6	0.0601	0.0226	2.6605	0.0078	0.0158	0.1044	23.7212	0.0026	0.0019	66.2749	2.9651
7	0.0486	0.0184	2.6442	0.0082	0.0126	0.0847	21.0271	0.0071	0.0014	61.9539	2.6284

8	0.0438	0.0166	2.6455	0.0082	0.0114	0.0763	17.505	0.0253	0.001	54.2989	2.1881
9	0.0484	0.0182	2.6532	0.008	0.0126	0.0841	20.7307	0.0079	0.0013	61.4098	2.5913
10	0.061	0.0241	2.5344	0.0113	0.0138	0.1081	23.4956	0.0028	0.0022	65.951	2.9369

Fail-safe N Calculation Using the Rosenthal Approach

Observed Significance Level: <.0001
Target Significance Level: 0.05
Fail-safe N: 131

Trim-and-fill analysis

Estimated number of missing studies on the left side: 3 (SE = 1.8667)

Random-Effects Model (k = 11; tau^2 estimator: DL)

tau^2 (estimated amount of total heterogeneity): 0.0009 (SE = 0.0007)
tau (square root of estimated tau^2 value): 0.0294
I^2 (total heterogeneity / total variability): 65.12%
H^2 (total variability / sampling variability): 2.87

Test for Heterogeneity:
Q(df = 10) = 28.6690, p-val = 0.0014

Model Results:

```
estimate      se     zval     pval    ci.lb    ci.ub
  0.0377   0.0129   2.9318   0.0034   0.0125   0.0629      **

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Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```
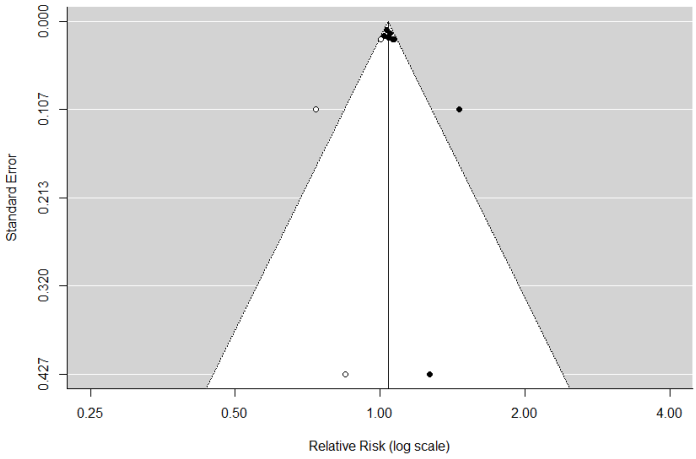
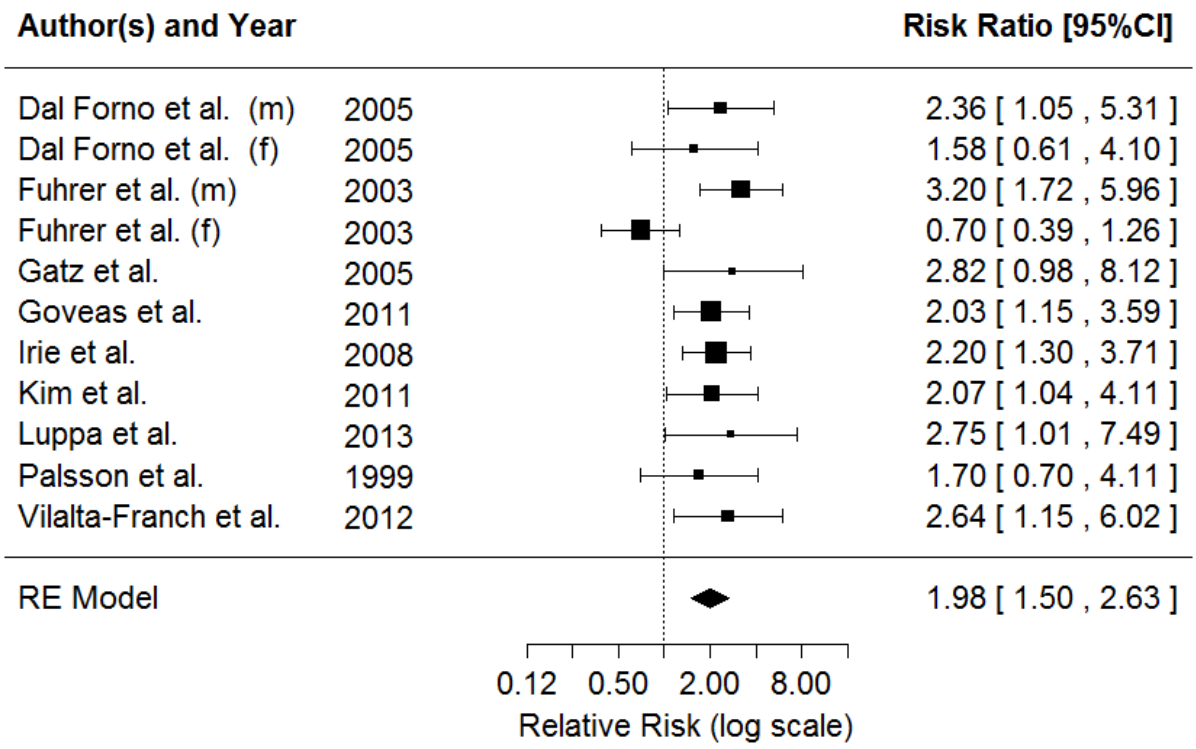



Dementia categorical (All compatible)



Random-Effects Model (k = 9; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
-6.6395	14.0693	17.2790	18.0748	18.7790

tau^2 (estimated amount of total heterogeneity): 0.0844 (SE = 0.0998)
tau (square root of estimated tau^2 value): 0.2905
I^2 (total heterogeneity / total variability): 38.34%
H^2 (total variability / sampling variability): 1.62

Test for Heterogeneity:
Q(df = 10) = 16.2182, p-val = 0.0936

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.6855	0.1441	4.7573	<.0001	0.4031	0.9679	***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.6725	0.157	4.2824	0	0.3647	0.9803	15.9913	0.0671	0.1034	43.7193	1.7768
2	0.704	0.155	4.5409	0	0.4001	1.0078	16.0193	0.0665	0.1014	43.8178	1.7799
3	0.6222	0.1476	4.2152	0	0.3329	0.9116	13.46	0.1429	0.0698	33.135	1.4956
4	0.8265	0.118	7.0026	0	0.5952	1.0579	2.8003	0.9717	0	0	1
5	0.666	0.1524	4.3692	0	0.3672	0.9648	15.7327	0.0727	0.0962	42.7944	1.7481
6	0.6865	0.1643	4.1774	0	0.3644	1.0087	16.1967	0.0629	0.1155	44.4332	1.7996
7	0.6745	0.165	4.0876	0	0.3511	0.9979	15.975	0.0674	0.115	43.662	1.775

8	0.6842	0.1607	4.2566	0	0.3691	0.9992	16.1867	0.0631	0.1098	44.3989	1.7985
9	0.6659	0.1531	4.3498	0	0.3658	0.9659	15.7466	0.0724	0.0969	42.8446	1.7496
10	0.7004	0.1565	4.4761	0	0.3937	1.0071	16.1187	0.0644	0.1039	44.1642	1.791
11	0.6627	0.1551	4.2715	0	0.3586	0.9668	15.6741	0.074	0.0984	42.5805	1.7416

Fail-safe N Calculation Using the Rosenthal Approach

Observed Significance Level: <.0001
Target Significance Level: 0.05
Fail-safe N: 142

Trim-and-fill analysis

Estimated number of missing studies on the left side: 4 (SE = 2.1937)

Random-Effects Model (k = 15; tau^2 estimator: DL)

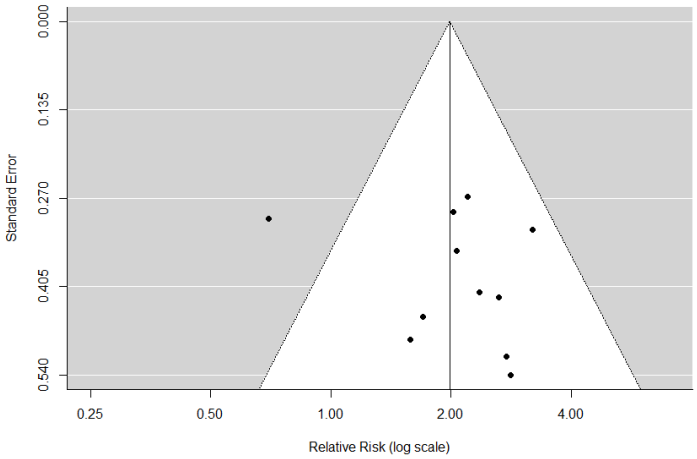
tau^2 (estimated amount of total heterogeneity): 0.1145 (SE = 0.0999)
tau (square root of estimated tau^2 value): 0.3384
I^2 (total heterogeneity / total variability): 44.24%
H^2 (total variability / sampling variability): 1.79

Test for Heterogeneity:
Q(df = 14) = 25.1089, p-val = 0.0335

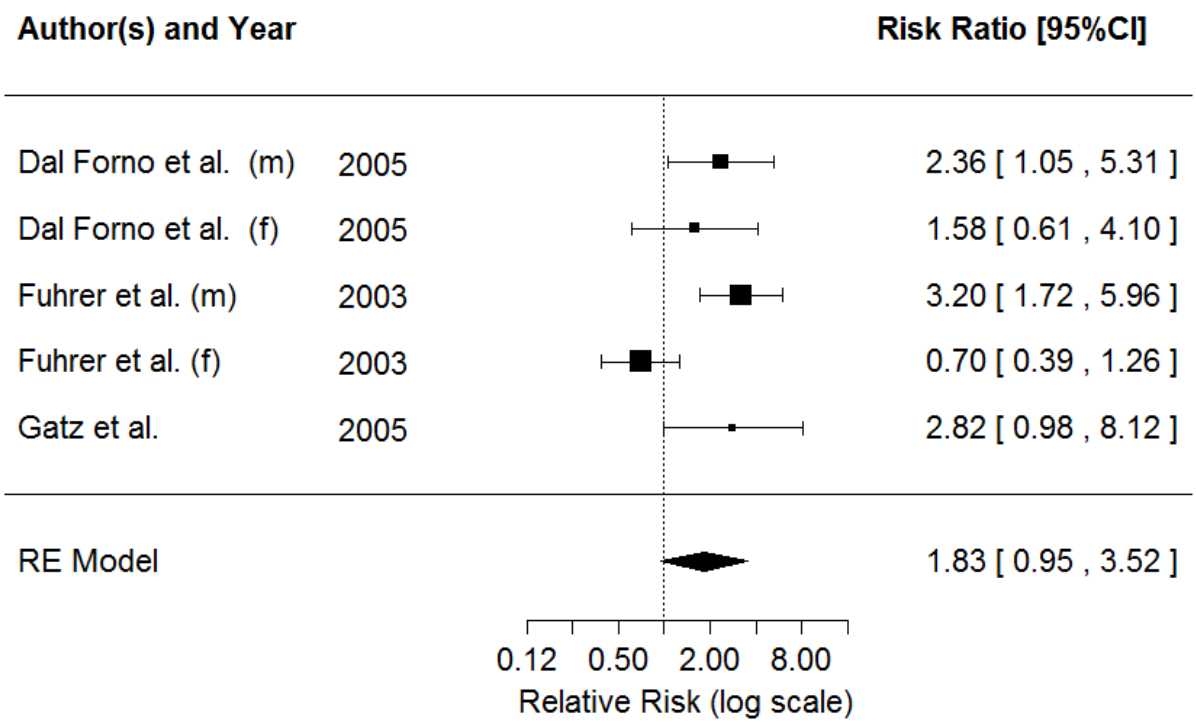
Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.5206	0.1344	3.8736	0.0001	0.2572	0.7840	***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1



Dementia categorical (CES-D >20)



Random-Effects Model (k = 5; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
-4.6477	9.2448	13.2954	12.5143	19.2954

tau^2 (estimated amount of total heterogeneity): 0.3891 (SE = 0.3983)
tau (square root of estimated tau^2 value): 0.6238
I^2 (total heterogeneity / total variability): 71.85%
H^2 (total variability / sampling variability): 3.55

Test for Heterogeneity:
Q(df = 4) = 14.2079, p-val = 0.0067

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.6033	0.3337	1.8080	0.0706	-0.0507	1.2574	.

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.5467	0.4162	1.3135	0.189	-0.2691	1.3625	13.4257	0.0038	0.5237	77.6548	4.4752
2	0.6427	0.4113	1.5627	0.1181	-0.1634	1.4487	14.1859	0.0027	0.5217	78.8523	4.7286
3	0.4305	0.3577	1.2035	0.2288	-0.2706	1.1316	8.5327	0.0362	0.3257	64.8412	2.8442

4	0.9413	0.2066	4.5557	0	0.5363	1.3462	1.5507	0.6706	0	0	1
5	0.5201	0.3882	1.3399	0.1803	-0.2407	1.2808	13.2095	0.0042	0.4585	77.289	4.4032

Fail-safe N Calculation Using the Rosenthal Approach

Observed Significance Level: 0.0005
Target Significance Level: 0.05
Fail-safe N: 16

Trim-and-fill analysis

Estimated number of missing studies on the left side: 1 (SE = 1.7009)

Random-Effects Model (k = 6; tau^2 estimator: DL)

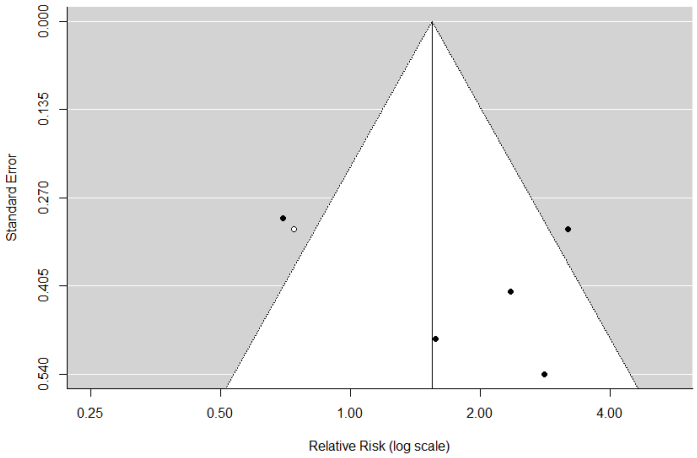
tau^2 (estimated amount of total heterogeneity): 0.4046 (SE = 0.3582)
tau (square root of estimated tau^2 value): 0.6361
I^2 (total heterogeneity / total variability): 74.33%
H^2 (total variability / sampling variability): 3.90

Test for Heterogeneity:
Q(df = 5) = 19.4798, p-val = 0.0016

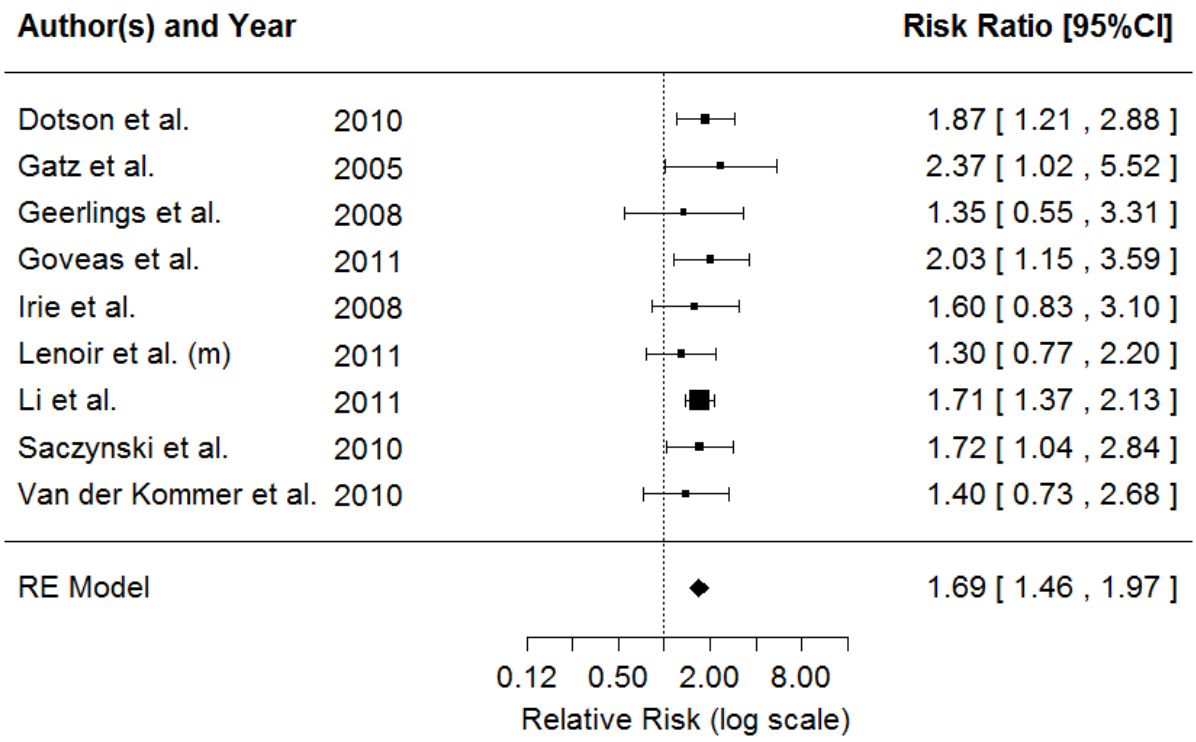
Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
0.4367	0.3056	1.4292	0.1529	-0.1622	1.0356

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1



Dementia categorical (CES-D >16)



Random-Effects Model (k = 9; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
1.7584	2.7745	0.4832	0.8776	2.4832

tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.0322)
tau (square root of estimated tau^2 value): 0
I^2 (total heterogeneity / total variability): 0.00%
H^2 (total variability / sampling variability): 1.00

Test for Heterogeneity:
Q(df = 8) = 2.7745, p-val = 0.9477

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.5268	0.0771	6.8328	<.0001	0.3757	0.6779	***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.5131	0.0823	6.2378	0	0.3519	0.6743	2.5459	0.9236	0	0	1
2	0.5157	0.0784	6.5817	0	0.3622	0.6693	2.1484	0.9512	0	0	1
3	0.5335	0.0782	6.8198	0	0.3801	0.6868	2.5213	0.9255	0	0	1
4	0.5131	0.08	6.4179	0	0.3564	0.6698	2.3577	0.9374	0	0	1
5	0.5299	0.0792	6.6914	0	0.3747	0.6852	2.7445	0.9076	0	0	1
6	0.5504	0.0805	6.8402	0	0.3927	0.7081	1.725	0.9735	0	0	1

7	0.5183	0.1058	4.8982	0	0.3109	0.7256	2.7606	0.9062	0	0	1
8	0.5253	0.0808	6.4972	0	0.3668	0.6837	2.7705	0.9054	0	0	1
9	0.5377	0.0793	6.7826	0	0.3824	0.6931	2.4244	0.9327	0	0	1

Fail-safe N Calculation Using the Rosenthal Approach

Observed Significance Level: <.0001
Target Significance Level: 0.05
Fail-safe N: 114

Trim-and-fill analysis

Estimated number of missing studies on the right side: 0 (SE = 2.0456)

Random-Effects Model (k = 9; tau^2 estimator: DL)

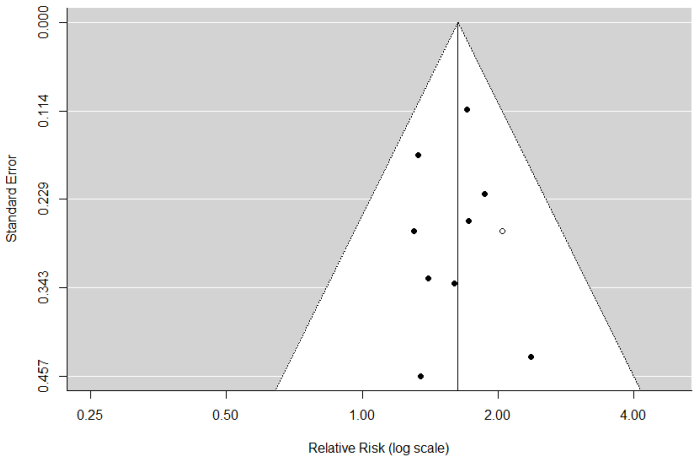
tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.0322)
tau (square root of estimated tau^2 value): 0
I^2 (total heterogeneity / total variability): 0.00%
H^2 (total variability / sampling variability): 1.00

Test for Heterogeneity:
Q(df = 8) = 2.7745, p-val = 0.9477

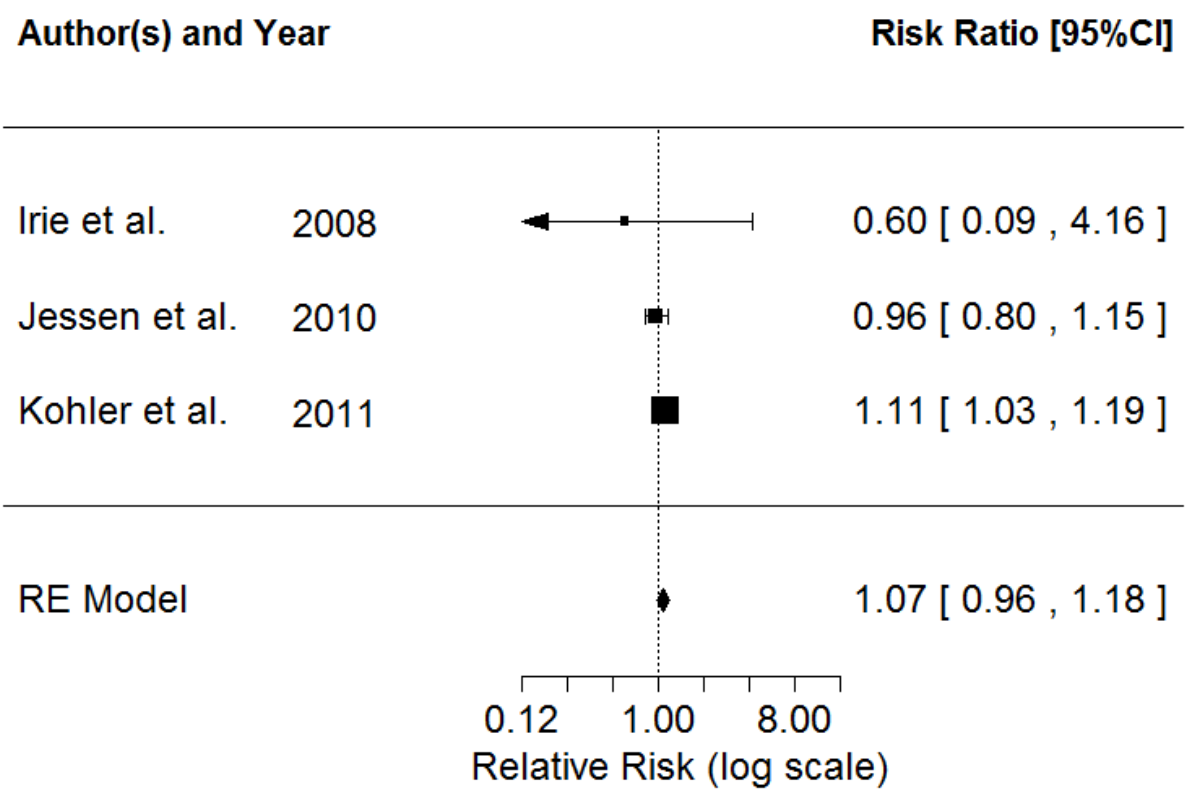
Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
0.5268	0.0771	6.8328	<.0001	0.3757	0.6779	***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1



VaD continuous (All)



Random-Effects Model (k = 3; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
1.3925	3.1371	1.2149	-0.5879	13.2149

tau^2 (estimated amount of total heterogeneity): 0.0027 (SE = 0.0124)
tau (square root of estimated tau^2 value): 0.0521
I^2 (total heterogeneity / total variability): 22.36%
H^2 (total variability / sampling variability): 1.29

Test for Heterogeneity:
Q(df = 2) = 2.5760, p-val = 0.2758

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
0.0631	0.0544	1.1599	0.2461	-0.0435	0.1696

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Leave one out sensitivity analysis

	estimate	se	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	0.5017	0.4457	1.1258	0.2602	-0.3717	1.3752	12.9869	0.0015	0.5039	84.5999	6.4934
2	0.4038	0.4305	0.938	0.3482	-0.44	1.2476	8.5973	0.0136	0.415	76.737	4.2987
3	0.9324	0.1994	4.6768	0	0.5417	1.3232	1.1598	0.56	0	0	1

4	0.5834	0.5536	1.0538	0.292	-0.5017	1.6685	13.4257	0.0012	0.7673	85.1032	6.7129

Fail-safe N Calculation Using the Rosenthal Approach

Fail-safe N Calculation Using the Rosenthal Approach
Observed Significance Level: 0.0003
Target Significance Level: 0.05
Fail-safe N: 14

Trim-and-fill analysis

Estimated number of missing studies on the left side: 1 (SE = 1.6103)

Random-Effects Model (k = 5; tau^2 estimator: DL)

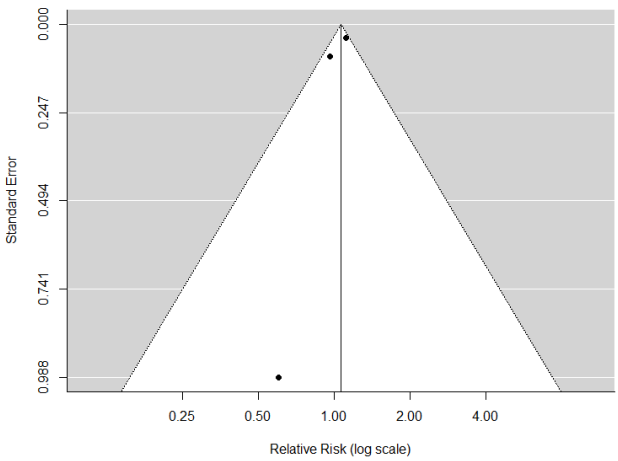
tau^2 (estimated amount of total heterogeneity): 0.4494 (SE = 0.4100)
tau (square root of estimated tau^2 value): 0.6704
I^2 (total heterogeneity / total variability): 80.15%
H^2 (total variability / sampling variability): 5.04

Test for Heterogeneity:
Q(df = 4) = 20.1561, p-val = 0.0005

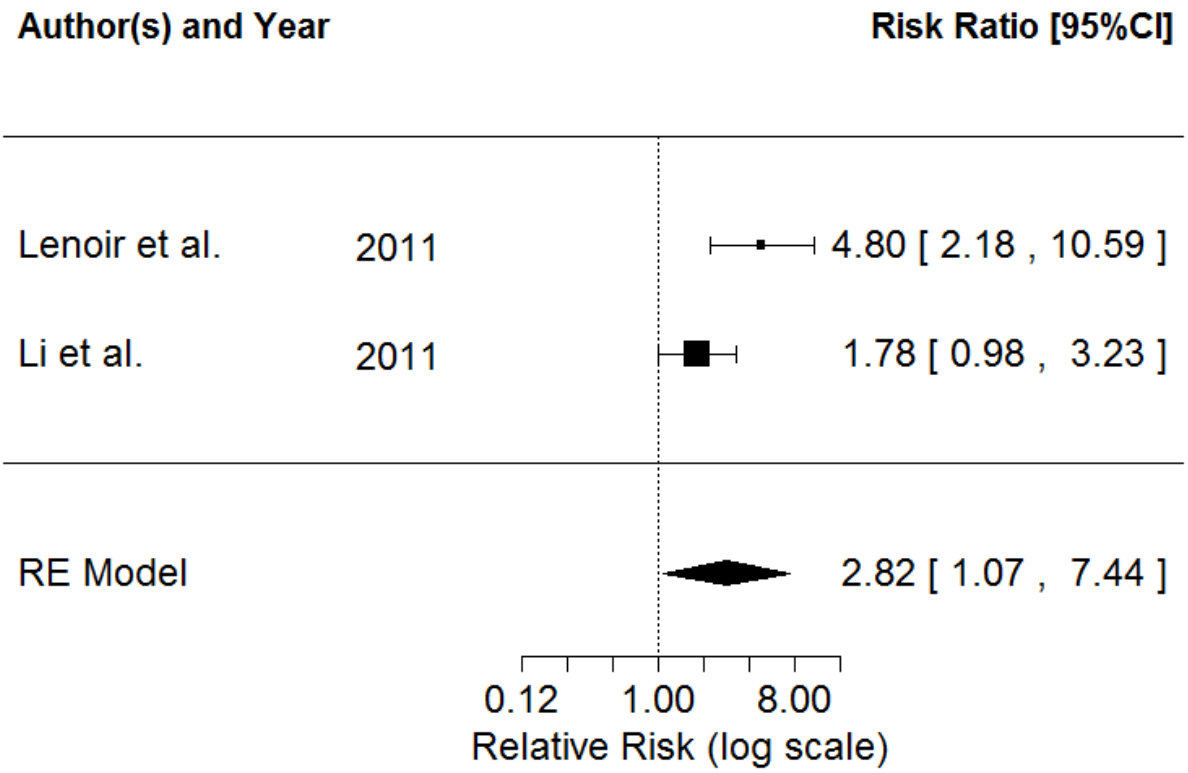
Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
0.4056	0.3388	1.1969	0.2313	-0.2585	1.0697

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1



VaD categorical (All)



Random-Effects Model (k = 2; tau^2 estimator: DL)

logLik	deviance	AIC	BIC	AICc
-1.6261	3.7765	7.2522	4.6385	19.2522

tau^2 (estimated amount of total heterogeneity): 0.3646 (SE = 0.6958)
tau (square root of estimated tau^2 value): 0.6038
I^2 (total heterogeneity / total variability): 74.10%
H^2 (total variability / sampling variability): 3.86

Test for Heterogeneity:
Q(df = 1) = 3.8603, p-val = 0.0494

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
1.0370	0.4947	2.0961	0.0361	0.0673	2.0066	*

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Fail-safe N Calculation Using the Rosenthal Approach

Fail-safe N Calculation Using the Rosenthal Approach
Observed Significance Level: <.0001
Target Significance Level: 0.05
Fail-safe N: 11